Additive Value of Heart Rate Variability in Predicting Obstructive Coronary Artery Disease Beyond Framingham Risk

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Background: Heart rate variability (HRV) is usually reduced in patients with CAD. We therefore investigated whether reduced HRV is predictive of angiographic CAD beyond Framingham risk in patients with stable angina.

Methods and Results: A total of 514 patients (age, 66.1±14.3 years, 358 men) were enrolled. Holter ECG was performed before catheterization, and 24-h HRV was analyzed in both the frequency domain (VLF, LF, HF and total power) and the time domain (SDNN, SDANN, RMSSD and pNN20). Angiographic CAD was defined as ≥50% diameter reduction of 1 or more coronary arteries. On coronary angiography 203 patients (39.6%) had angiographic CAD. Patients with CAD had significantly higher Framingham risk and lower HRV according to both frequency and time domain parameters. After controlling for age, gender, heart rate, SBP, renal function, lipids and Framingham risk, reduced HRV indices remained predictors of CAD (OR, 95% CI for LF, HF, SDNN, RMSSD and pNN20: 0.81, 0.66–0.99; 0.77, 0.63–0.94; 0.75, 0.59–0.96; 0.72, 0.58–0.88; and 0.76, 0.62–0.94, respectively). On subgroup analysis, HRV parameters appeared to be predictive of CAD only in subjects with high Framingham risk or diabetes.

Conclusions: Reduced HRV is predictive of CAD in patients with stable angina, independent of traditional risk factors and Framingham risk. The predictive value of HRV may be relevant only in subjects with high Framingham risk or diabetes. (Circ J 2016; 80: 494–501)

Key Words: Coronary artery disease; Heart rate variability

Coronary artery disease (CAD) is the most common type of heart disease. Coronary angiography (CAG) and intervention are the standard treatment for evaluation of coronary anatomy and, further, to alleviate their symptoms and even prevent future acute coronary syndrome (ACS).1-3 Such an invasive diagnostic procedure, however, does not appear to be suitable, given that, in an American College of Cardiology registry involving 398,978 patients, only 37.6% of the patients who had undergone CAG had obstructive CAD.4 Heart rate variability (HRV) is a non-invasive marker for the autonomic nervous system.5,6 The generality of time-domain indices of HRV are usually calculated from 24-h recording of heart rate, but the frequency-domain indices could be derived from either 24-h or as short as 2-min electrocardiographic (ECG) recordings.6 Kotecha et al showed that low HRV from 5-min ECG recordings immediately before CAG was strongly predictive of angiographic CAD.7 Transient perturbations of HRV introduced by some manipulations and emotional or physical stress in the catheterization laboratory, however, might not be negligible.5 In addition, the presence of myocardial infarction, significant valvular heart disease, and impaired left ventricular function in their subjects could also confound the measurement of HRV.7

We therefore conducted this study to investigate whether HRV could predict angiographic CAD beyond traditional risks in patients with stable angina, using 24-h ECG recording, and
to further elucidate the variations between time-domain and frequency-domain HRV indices.

Methods

Subjects

The subjects were selected from an intramural registry of Taipei Veterans General Hospital (TARGET registry), conducted to enroll patients with clinical impression of CAD. In addition to treadmill exercise test, ambulatory ECG monitoring, echocardiography, medical history, physical examinations, and biochemistry were also prospectively logged in a Web-based electronic medical recording system. Estimated glomerular filtration rate (eGFR) was calculated using the published formula for Chinese subjects, and Framingham 10-year event risk was also calculated accordingly.

Subjects with positive non-invasive stress test and CAG within 6 months were eligible, while patients with heart failure, previous myocardial infarction, or documented CAD on CAG were excluded. From 2009 to 2013, we collected data on a total of 767 patients with stable angina, who had received 24-h ambulatory ECG monitoring using the same system (Medilog FD4, Oxford Instruments, UK). The final subject group consisted only of patients with sinus rhythm (Figure 1). The investigation conformed to the principles outlined in the Declaration of Helsinki, and the institutional review board of Taipei Veterans General Hospital approved the study.

Analysis of HRV

Holter recording for up to 24 h was carried out using 3-channel digital recorders (Medilog FD4). When at least 18 h of good quality ECG signals were obtained, the ECG signals were then automatically processed and scrutinized using open-source HRV algorithms to conduct standard HRV analyses of the heartbeats. In contrast, the intervals between ectopic beats, between normal and ectopic beats, and between the unrecognizable beats were excluded from analysis. Patients with rejected intervals >5% of the total recordings were excluded from the study. Briefly, the time-domain measures of HRV consisted of mean heart rate and standard deviation of the normal interbeat intervals (SDNN), the root mean square of the successive difference between adjacent normal interbeat intervals (RMSSD), and the percentage of adjacent intervals that varied by >20 ms (pNN20), which is more discriminative for pathologic conditions than pNN50. SDNN gauges the overall variability of interbeat intervals. RMSSD and pNN20 rank the short-term variations of interbeat intervals, which are mainly regulated by parasympathetic innervation.

In contrast, standard spectral HRV measures included high-frequency power (HF; 0.15–0.40 Hz), low-frequency power (LF; 0.04–0.15 Hz), and very low-frequency power (VLF; 0.003–0.04 Hz). The spectral HRV data were transformed using the natural logarithm for statistical analysis.

Definition of CAD

CAG was performed with at least 6 standardized projections of the left coronary artery and 2 of the right coronary artery. We classified the angiographic results into 3 categories: normal; non-obstructive CAD; and angiographic CAD (defined as ≥50% diameter reduction in 1 or more native epicardial coronary arteries or main tributary). Two independent and experienced interventionists, who were blinded to patient characteristics, reviewed all angiograms, with decision by senior physician in the case of differences in interpretation.

Statistical Analysis

Data are given as mean±SD or n (%). The 3 groups were compared via 1-way ANOVA and post-hoc Bonferroni test for continuous variables. Categorical variables were compared using the chi-squared test. Predictors of CAD were investigated using logistic regression analysis, and the independence of each HRV indices was tested on multiple logistic regression analysis.
obstructive CAD, we used receiver operating characteristic (ROC) curve analysis, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). The diagnostic accuracy of each model was calculated using discriminant analysis. On ROC curve analysis 409.1 ms² and 404.6 ms² were identified as cut-offs of HF and LF power, respectively, in the total population to predict CAD. The probability of angiographic CAD according to Framingham 10-year absolute event risk and HRV was compared using chi-squared test. On subgroup analysis, age was controlled for in order to evaluate the independent associations of HRV with CAD. Sensitivity

<table>
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<tr>
<th>Table 1. Subject Baseline Characteristics</th>
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<tr>
<td>Normal coronary artery</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Male gender (%)</td>
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<tr>
<td>SBP (mmHg)</td>
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<td>DBP (mmHg)</td>
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</table>

Comorbidities

- Hypertension: 54 (34.6) vs. 84 (53.5)*† vs. 132 (64.7)*† |
- Diabetes: 23 (14.7) vs. 44 (28)*† vs. 83 (40.7)*† |
- Hyperlipidemia: 24 (15.4) vs. 43 (27.4)*† vs. 59 (28.9)*† |
- Smokers: 35 (22.4) vs. 53 (33.8)*† vs. 77 (37.7)*† |
- Total cholesterol (mg/dl): 171.3±30.7 vs. 180.6±34.8*† vs. 171.7±32.7*† |
- LDL-C (mg/dl): 49.4±15.4 vs. 48.8±14.9 vs. 43.9±14.1*† |
- eGFR (ml/min/1.73 m²): 93.8±27.8 vs. 88±27.6 vs. 76.7±32.7*† |
- Framingham risk (%): 8.4±6.1 vs. 14.3±9.7*† vs. 18.7±11.8*† |

<table>
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<tr>
<th>Table 2. Heart Rate and HRV vs. Angiography Findings</th>
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<tr>
<td>Normal coronary artery</td>
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<tr>
<td>Mean heart rate (beats/min)</td>
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</table>

Frequency-domain variables

- VLF power (ms²): 8.25±0.90 vs. 8.11±0.99 vs. 7.92±0.83*† |
- LF power (ms²): 6.93±1.08 vs. 6.75±1.13 vs. 6.50±1.04*† |
- HF power (ms²): 6.71±1.25 vs. 6.49±1.35 vs. 6.31±1.29*† |
- TP (ms²): 8.70±0.92 vs. 8.55±0.95 vs. 8.36±0.85*† |
- LF/HF: 2.06±1.47 vs. 2.24±1.83 vs. 1.98±1.34 |

Time-domain variables

- SDNN (ms): 109.64±39.41 vs. 103.87±35.62 vs. 94.73±32.82*† |
- SDANN (ms): 93.81±37.75 vs. 87.73±33.97 vs. 80.59±31.12*† |
- RMSSD (ms): 41.31±24.77 vs. 39.68±26.12 vs. 35.77±22.38*† |
- pNN20 (%): 41.02±19.42 vs. 38.62±20.19 vs. 34.87±19.51*† |

Data given as mean±SD or n (%). *P<0.05 (†vs. normal coronary artery subjects; ‡angiographic CAD vs. non-obstructive CAD). CAD, coronary artery disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RAS blockers, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; SBP, systolic blood pressure.


Table 3. Predictors of Angiographic CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
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<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Frequency-domain variables</td>
<td></td>
<td></td>
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<tr>
<td>VLF power (1 SD=0.9 ms²)</td>
<td>0.85 (0.68–1.05)</td>
<td>0.138</td>
</tr>
<tr>
<td>LF power (1 SD=1 ms²)</td>
<td>0.80 (0.65–0.99)</td>
<td>0.035</td>
</tr>
<tr>
<td>HF power (1 SD=1.3 ms²)</td>
<td>0.76 (0.62–0.93)</td>
<td>0.009</td>
</tr>
<tr>
<td>TP (1 SD=0.9 ms²)</td>
<td>0.81 (0.65–0.99)</td>
<td>0.043</td>
</tr>
<tr>
<td>Time-domain variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (1 SD=36.2 ms)</td>
<td>0.74 (0.58–0.94)</td>
<td>0.015</td>
</tr>
<tr>
<td>SDANN (1 SD=34.5 ms)</td>
<td>0.83 (0.66–1.06)</td>
<td>0.134</td>
</tr>
<tr>
<td>RMSSD (1 SD=24.4 ms)</td>
<td>0.71 (0.58–0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>pNN20 (1 SD=19.8%)</td>
<td>0.75 (0.61–0.92)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Natural logarithm transformed. Model 1 controlling for age, gender, SBP, eGFR, HDL-C, heart rate; model 2 controlling for age, gender, SBP, eGFR, HDL-C, heart rate, Framingham risk. Abbreviations as in Tables 1, 2.

Results

Among the total of 514 subjects (66.1±14.3 years, 154 women), 203 patients (39.5%) had angiographic CAD, 157 patients (30.5%) had non-obstructive CAD, and the other 154 patients (30%) had normal coronary arteries. Baseline characteristics are listed in Table 1. In addition to conventional risk factors, SDNN, SDANN, RMSSD, pNN20, VLF power, LF power, HF power and total power significantly decreased in the order of normal coronary artery, non-obstructive CAD, and angiographic CAD (Table 2). Meanwhile, LF/HF was similar between the groups.

Predictors of Obstructive CAD

Advanced age, male gender, SBP, eGFR, HDL-C, and Framingham risk correlated with the presence of angiographic CAD.
CAD, while the total cholesterol and low-density lipoprotein cholesterol did not (data not shown). Except for LF/HF ratio, all the other HRV indices were predictors of obstructive CAD, while patients who had high HRV indices were less likely to have angiographic CAD. LF power, HF power, and total power, as well as SDNN, RMSSD, and pNN20 remained independent predictors when age, gender, heart rate, SBP, eGFR, and HDL-C were controlled for (Table S2). After further controlling for Framingham risk, the correlations remained (Table 3, model 2). With fixed adjustments for conventional risk factors in a forward stepwise logistic regression analysis among frequency-domain HRV variables, HF power was the strongest predictor in the model. Again among the time-domain HRV variables, RMSSD had the greatest added value in this forward stepwise logistic regression analysis. Both HF power and RMSSD consistently correlated with angiographic CAD, independent of conventional risks, comorbidity, and prescribed medication (Table S1).

On subgroup analysis, reduced HF power was related to angiographic CAD, independent of age, especially in high Framingham risk or diabetic subjects. Both of the interactions between Framingham risk or diabetes with HF power in predicting CAD were significant (P=0.024 and 0.013), respectively (Figure 2). In contrast, the prediction of angiographic CAD by HF power was not significantly affected by age, gender, smoking habit, hypertension, or use of β-blockers.

On ROC curve analysis, HF power did not improve the diagnostic probability of angiographic CAD on top of Framingham risk in either the high-risk patients (P=0.077) or in the total group (Figure 3). HF power, however, did offer additional risk stratification with respect to the Framingham risk algorithm (Figure 4). On discriminant analysis the HRV indices improved the diagnostic accuracy on top of absolute 10-year Framingham risk score in the total group and especially in the high Framingham risk (>20%) subjects (Table 4). The addition of HF or LF power to Framingham risk in the prediction model indeed offered significant NRI of 31.1% in the high-risk group (Table 4). Although none of the HRV indices provided substantial NRI beyond Framingham risk alone in the whole subject group, all of the HRV indices produced considerable clinical NRI and IDI in the total group and in the high-risk group (Table 4).

**Sensitivity Analysis**

Among 437 subjects (85% of the total group) who had CAG within 90 days after Holter recording, the HRV indices remained independent predictors of angiographic CAD, after controlling for age, gender, SBP, and HDL-C (Table S2).

**Discussion**

The major findings of this study are as follows: (1) both frequency-domain and time-domain HRV indices were independently associated with angiographic CAD; (2) HRV indices were related to CAD in various subgroups, but there might be significant interactions between patients with and without high Framingham risk or diabetes; (3) reductions of HRV may provide incremental predictive value in predicting CAD especially in high-risk patients. The results expand our understanding of the association between autonomic activity and CAD and support the clinical applications of HRV in the evaluation of CAG indications.

Reduction of HRV has been considered to represent a breakdown of sympathetic and parasympathetic modulation, which is related to the progression of coronary atherosclerosis and the presence of CAD.14-17 A population-based, prospective study suggested that altered cardiac autonomic activity, especially lower parasympathetic activity, is associated with the risk of developing CAD.18 In a case-control study, Hayano et al also reported that reduced vagal activity correlated with the severity of CAD,19 which is consistent with the present findings. Moreover, of the HRV parameters, HF power and
HRV and CAD

RMSSD improved the model predictive probability the most. Confounders have been identified to affect cardiac autonomic function, especially left ventricular function. In the Kotecha et al study, one-third of the patients with angiographic CAD had myocardial infarction, 20% of them had impaired left ventricular function, and >24% had abnormal rhythm; all would confound the measures of HRV. In contrast, this study excluded patients with known heart failure or myocardial infarction, existing CAD, or rhythm disorders. On multiple logistic regression analysis the predictive value of HRV was independent of traditional risk factors, comorbidities, and the use of cardiovascular drugs. Although it is difficult to relate specific HRV measures to either sympathetic or parasympathetic tone, the present study has shown that both frequency-domain and time-domain HRV are predictive of CAD in patients with stable angina.

There is growing use of short-term measures of HRV to evaluate clinical outcomes in the general population and in patients with myocardial infarction. The pre-procedural measures of HRV from 5-min ECG recordings are able to predict the following CAG results, regardless of morbidity, medication, and ECG abnormalities. The reproducibility of short-term HRV remains a controversy, however, while autonomic activity varies within 1 day and can be affected even by acute mental stress. Given that patients undergoing CAG may face mental stress due to having an invasive examination, the predictions may differ in different patients, pre-procedural settings, and even the temperature in the catheterization room. Miyase et al showed that 5-min HRV was predictive of CAD only when it was measured immediately but not 1 day before CAG. In addition, as a tool of prediction, immediate pre-procedural measures may introduce no change to clinical decisions. In contrast, HRV derived from 24-h Holter ECG are stable and reproducible across a long follow-up period and

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<th>Table 4. Improvement in Prediction of Angiographic CAD by Incorporating HRV Into Framingham 10-Year Event Risk Score</th>
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<tbody>
<tr>
<td><strong>Classified accuracy (%)</strong></td>
</tr>
<tr>
<td>Total group</td>
</tr>
<tr>
<td>Framingham risk</td>
</tr>
<tr>
<td>+HF power</td>
</tr>
<tr>
<td>+LF power</td>
</tr>
<tr>
<td>+TP power</td>
</tr>
<tr>
<td>+SDNN</td>
</tr>
<tr>
<td>+RMSSD</td>
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<tr>
<td>+pNN20</td>
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*P<0.05. †Framingham 10-year event risk score >20%. (c)NRI, (clinical) net reclassification improvement; IDI, integrated discrimination improvement; RMSSD, root mean square of the successive difference between adjacent normal interbeat intervals. Other abbreviations as in Tables 1,2.

Figure 4. Probability of angiographic coronary artery disease according to Framingham 10-year absolute event risk and high-frequency (HF) power.
even after invasive treatment.\textsuperscript{28,29} Although the study indicated that 24-h HRV analysis might improve the clinical decision-making with regard to CAG, the feasibility was low. But if patients have undergone 24-h ECG recording for other reasons, it could be valuable to assist with CAD prediction.

The present study also demonstrated significant interactions of HRV in predicting angiographic CAD in the patients with or without high Framingham risk >20\%, and in patients with or without diabetes. In short, patients without diabetes did not have improvements in prediction of CAD with HF or LF power. The findings are in line with those of Karjalainen et al, who found that the prognostic impact of autonomic function in CAD was very small in non-diabetic subjects.\textsuperscript{30} Moreover, reduced HF power as well as LF power independently correlated with angiographic CAD, after controlling for age in patients with high Framingham risk or diabetes rather than in those without (Figures S1–S3). There was a significant improvement in risk reclassifications by modeling HRV in the prediction model of angiographic CAD in high Framingham risk patients. Given that diabetes has long been recognized as a myocardial infarction-equivalent risk,\textsuperscript{31} the present study supports HRV as a remarkable predictor of CAD, especially in high-risk patients.

**Study Limitations**

Given the nature of observational studies, there are several limitations. First, the subject group was drawn from a registry, and not all of the participants were required to undergo Holter study, hence there would be selection biases. Second, there was a considerable time lag between Holter ECG and CAG, introducing the possibility of maturation bias to internal validity. The available data, however, suggest the high stability of HRV measures derived from 24-h ambulatory ECG monitoring in both healthy subjects and in the CAD subjects.\textsuperscript{28,32}\textsuperscript{33} In addition, the study results consisted of both time-domain and frequency-domain measures of HRV, and the results were confirmed further by sensitivity test. Third, we did not evaluate the myocardial damage, if any, which might confound the measure of HRV. None of the subjects, however, had past clinical events of myocardial damage, given that we excluded patients with either heart failure or previous myocardial infarction. Fourth, we used pNN20 rather than the commonly used pNN50 as an HRV index. Last, we did not analyze the relationship between CAD territories and HRV, although right coronary artery lesions might affect heart rate.

**Conclusions**

The measures of HRV are associated with angiographic CAD in patients with stable angina, independent of traditional risk factors, comorbidity, medication, and Framingham risk. In addition, in patients with high risk of CAD, HRV were even more predictive. Measures of HRV may provide specific advantages in clinical practice to improve the risk reclassification of angiographic CAD. Given the inconvenience of 24-h ECG recordings, the benefit and feasibility of using Holter ECG to optimize the diagnostic algorithm of CAD remain important.

**Acknowledgments**

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**Disclosures**

The authors declare no conflicts of interest.

Supplementary Files

Supplementary File 1

Table S1. Independence of HRV indices in predicting angiographic CAD

Table S2. Sensitivity analysis† for the predictors of angiographic CAD in subjects with 24-h ECG and CAG within 90 days (n=437)

Figure S1. Odds ratios per increment of 1 SD of low-frequency power (LF; 1 SD=1.3 ms²) for the presence of obstructive coronary artery disease in the younger (≤65 years) and the older (>65 years) subjects; in women and men; in subjects with Framingham risk ≤20%; and in subjects with and without smoking, hypertension, diabetes, or use of β-blockers after controlling for age.

Figure S2. Receiver operator curves (ROC) comparing (red line) Framingham 10-year absolute event risk of total CAD and low-frequency (LF) power heart rate variability index in the (A) total group and (B) in the patients with Framingham 10-year absolute event risk >20%.

Figure S3. Probability of obstructive coronary artery disease (CAD) according to Framingham 10-year absolute event risk of total CAD and low-frequency (LF) power.

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-15-0588