# Heart Rate Variability and Progression of Coronary Atherosclerosis

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***Abstract***—Low heart rate (HR) variability is associated with increased risk of cardiovascular morbidity and mortality, but the causes and mechanisms of this association are not well known. This prospective study was designed to test the hypothesis that reduced HR variability is related to progression of coronary atherosclerosis. Average HR and HR variability were analyzed in 12-hour ambulatory ECG recordings from 265 qualified patients participating in a multicenter study to evaluate the angiographic progression of coronary artery disease in patients with prior coronary artery bypass surgery and low high-density lipoprotein cholesterol concentrations (<1.1 mmol/L). Participants were randomized to receive a placebo or gemfibrozil therapy. The progression of coronary atherosclerosis was estimated by quantitative, computer-assisted analysis of coronary artery stenoses from the baseline angiograms and from repeated angiograms performed an average of 32 months later. The progression of focal coronary atherosclerosis of the patients randomized to placebo therapy was more marked in the tertile with the lowest standard deviation of all normal to normal R-R intervals (SDNN, 74±13 ms; mean decrease in the per-patient minimum luminal diameter −0.17 mm; 95% confidence interval [CI], −0.23 to −0.12 mm) than in the middle tertile (SDNN, 107±7 ms; mean decrease −0.05 mm; 95% CI, −0.08 to −0.01 mm) or highest tertile (SDNN, 145±25 ms; mean change 0.01 mm; 95% CI, −0.04 to 0.02 mm) ($P<0.001$ between the tertiles). This association was abolished by gemfibrozil. SDNN was lower ($P<0.001$) and minimum HR was faster ($P<0.01$) in the patients with marked progression than in those with regression of focal coronary atherosclerosis. In multiple regression analysis including HR variability, minimum HR, demographic and clinical variables, smoking, blood pressure, glucose, lipid measurements and lipid-modifying therapy, progression of focal coronary atherosclerosis was independently predicted by the SDNN ($\beta=0.24$; $P=0.0001$). Low HR variability analyzed from ambulatory ECG predicts rapid progression of coronary artery disease. HR variability provided information on progression of focal coronary atherosclerosis beyond that obtained by traditional risk markers of atherosclerosis. **(*Arterioscler Thromb Vasc Biol.* 1999;19:1979-1985.)**

**Key Words:** coronary artery disease ■ lipids ■ heart period ■ angiography

Elevated heart rate (HR) and reduced HR variability are associated with an increased risk of cardiovascular morbidity and mortality in various populations,[1–8] but the pathophysiological link between these associations is not well understood. Experimental studies on monkeys fed an atherogenic diet have demonstrated a relationship between resting HR and progression of coronary atherosclerosis,[9–11] and there is also a strong relationship between HR and arterial stiffness,[12] but there has been little evidence of any association between HR, or its variability, and human coronary atherosclerosis.

Progression of coronary artery stenoses in repeated coronary angiograms increases the risk of adverse cardiac events, suggesting that rapid progression predisposes patients to acute complications of coronary artery plaques and serves as a surrogate end point for clinical events.[13,14] Lipid-modifying therapy has been shown to prevent the progression of coronary atherosclerosis, confirming that abnormalities in plasma lipid concentrations are strongly associated with the progression of coronary artery disease and the occurrence of adverse clinical events.[14] However, lipid theory may not explain all aspects of coronary artery disease, eg, the rapid progression of discrete stenoses in specific coronary arterial regions, which is thought to result from an interplay of hemodynamic, metabolic, and hemostatic factors.[15–18] To test the hypothesis that elevated HR and reduced HR variability are associated with the progression of human coronary atherosclerosis in patients with lipid abnormalities, we studied HR and its variability, measured by ambulatory ECG, and the angiographic progression of coronary artery disease in patients with reduced HDL cholesterol concentrations.

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# Methods

## Patients and Study Protocol

Three-hundred and five men aged <70 years, randomized in a double-blind fashion to receive either slow-release gemfibrozil or a matching placebo in the Lopid Coronary Angiography (LOCAT) trial, underwent ambulatory ECG recordings before the baseline angiographic examination. The inclusion and exclusion criteria have been described in detail recently.[19] In brief, all the patients had previously undergone coronary bypass surgery, and they also fulfilled the following inclusion criteria at two consecutive screening visits: HDL cholesterol ≤1.1 mmol/L, LDL cholesterol ≤4.5 mmol/L, and serum triglycerides ≤4.0 mmol/L. In addition, they had blood pressure ≤160/95 mm Hg, body mass index ≤30 kg/m$^2$, left ventricular ejection fraction ≥35%, no history of diabetes, fasting glucose concentration <7.8 mmol/L, and no condition requiring therapy with calcium channel blockers, ACE inhibitors, or diuretics. Details of the entry criteria and screening process, clinical visits, and laboratory analyses have been described previously.[19,20] All patients provided written informed consent, and the study was approved by the ethics committees of the participating hospitals. All the patients underwent comprehensive clinical examinations, bicycle exercise tests, and received detailed dietary counseling at the baseline stage. Fasting serum triglycerides, cholesterol, HDL and LDL cholesterol, and blood glucose were measured by methods described previously.[19,20]

## Coronary Angiography

Native coronary arteries and bypass grafts were imaged at baseline and at the end of the trial (32±3 months after the baseline angiogram) as described previously.[19–21] The images were analyzed with the Cardiovascular Measurement System (Medis) by a single trained technical analyst. The accuracy and reproducibility of the angiographic analyses have been shown to be comparable to those reported previously by other investigators.[21] All angiographic analyses and handling of the data were done by persons blinded to the treatment group and ambulatory ECG data.

The progression of atherosclerosis was defined by measuring the change from the baseline to the follow-up angiogram in the average diameter of the coronary artery segments and the minimum luminal diameter of the discrete stenoses. Per-patient means of these variables were calculated in 3 types of native coronary segments, differing in their relation to the bypass grafts, ie, unaffected, graft affected (proximal to graft insertions and hemodynamically related), and graft-dependent (distal to graft insertions). Per-patient means were also calculated for the average and minimal diameters in all native segments. New lesions were defined as stenoses in the follow-up angiogram causing at least 20% diameter reduction that were not present on the baseline angiogram.

## HR Variability Analyses

The prospective study of the effects of HR variability on progression of coronary artery disease was performed by recording ambulatory ECG after informed consent on the day before the baseline coronary angiography, or 1 day after the angiography. Patients with acute cardiovascular events, ie, myocardial infarction, unstable angina pectoris, or stroke between the baseline and repeat angiogram; patients with atrial fibrillation; and those with technically inadequate ECG recordings were excluded. After exclusions, 265 patients were included in the study. Ambulatory ECG recordings were performed between 6 PM and 10 AM, including at least 4 hours awake and 4 hours asleep.

The ECG data were sampled digitally and transferred from the Oxford Medilog scanner to a microcomputer for analysis of HR variability.[22] All the R-R interval time series were first edited automatically, after which careful manual editing was performed by visual inspection of the R-R intervals. Each R-R interval time series was passed through a filter that eliminates premature beats and artifacts, and deletes the filling gaps, using previously described methods.[22,23] Only recordings with qualified beats for at least a 12-hour period, and with >85% of qualified sinus beats, were included in the analysis of HR variability (n=265).

After editing of the R-R interval tachograms, the R-R interval spectra were generated. A Fast Fourier transform method was used to estimate the power spectrum densities of HR variability.[23] Frequency domain measures of R-R interval variability were computed by integrating the point-power spectrum over the frequency intervals. The power spectra were quantified by measuring the areas in the following frequency bands: (1) <0.0033 Hz (ultra-low frequency power), (2) 0.0033 to <0.04 Hz (very low frequency power), (3) 0.04 to 0.15 Hz (low frequency power), and (4) 0.15 to <0.4 Hz (high frequency power). The standard deviation of all normal-to-normal R-R intervals (SDNN) was used as a time-domain measure of HR variability. The average HR was measured for each hour of the recording period, and the minimum, maximum, and average R-R intervals were calculated.

## Statistical Analyses

The patients were divided into tertiles according to the baseline HR variability, and ANOVA followed by Bonferroni post-hoc analysis was used to compare the continuous variables between these tertiles. ANCOVA was used for adjustments for possible confounding effects of various variables on differences between the groups. Pearson's correlation coefficients were used to estimate the linear correlations between continuous variables. The $\chi^2$ test was used to compare categorical variables. Linear multiple regression analysis (stepwise forward analysis, SPSS for Windows, version 6.0) was used to assess the predictors of the progression of coronary atherosclerosis. Data are presented as mean±standard deviation (SD) in all Tables.

# Results

## Relation of Baseline Characteristics to HR Variability

Patients were divided into tertiles according to baseline HR variability; SDNN was 74±13 ms in the lowest tertile, 104±7 ms in the middle tertile, and 145±25 ms in the highest tertile. Baseline demographic characteristics, history and symptoms of heart disease, cardiac medication, results of exercise tests, number of randomized patients, and laboratory data are shown in Table 1. The blood glucose level was higher in the tertile with the lowest SDNN than in the highest tertile, but no other variable, eg, age, blood pressure, lipid values, duration of coronary artery disease, medication, presence of angina pectoris, ischemia during exercise test (Table 1), or left ventricular ejection fraction (Table 2), differed across the tertiles.

## Angiographic Progression of Coronary Artery Disease

The progression of coronary artery stenoses, as assessed from the per-patient decrease in the minimum luminal diameter of all native vessels, was more marked in the patients with the lowest SDNN than in the middle and highest tertile (Figure 1). This difference was observed as a per-patient change in all native segments, −0.11 mm (95% CI, −0.15 to −0.07 mm) in the lowest tertile, −0.06 mm (95% CI, −0.09 to −0.04 mm) in the middle tertile, and −0.03 mm (95% CI, −0.06 to 0.001 mm) in the highest tertile ($P<0.01$ between the tertiles); the difference was evident in both the native vessels without bypass grafts and the proximal portions of grafted native vessels (Table 2) but not in the grafted distal coronary artery segments. The difference in the per-patient change in minimal luminal diameter remained significant among the HR variability tertiles after adjustments to all baseline variables, including randomization to lipid-modifying therapy (ANCOVA, F=4.7, $P=0.01$). In the total study group, a significant correlation existed between the

**TABLE 1. Baseline Characteristics, Laboratory, and Angiographic Data on the Patients**

| | SDNN 31–90 ms (n=88) | SDNN 91–117 ms (n=89) | SDNN 118–250 ms (n=88) |
|---|---|---|---|
| Age, y | 60 (6) | 59 (7) | 58 (8) |
| Blood pressure | | | |
| Systolic (mm Hg) | 136 (18) | 135 (17) | 136 (17) |
| Diastolic (mm Hg) | 83 (8) | 83 (8) | 82 (8) |
| BMI (kg/m$^2$) | 26.9 (2.2) | 26.3 (2.1) | 26.2 (2.4) |
| Waist/hip ratio | 0.95 (0.04) | 0.93 (0.04) | 0.94 (0.04) |
| Time from CABG (mo) | 23 (13) | 23 (13) | 22 (12) |
| Duration of AP before CABG (mo) | 7.4 (5.6) | 6.0 (5.1) | 5.9 (4.0) |
| History of AMI | 42 (48%) | 45 (50%) | 49 (56%) |
| Smokers | 5 (6%) | 5 (6%) | 2 (2%) |
| Beta-blocking medication | 67 (76%) | 69 (78%) | 63 (72%) |
| Symptoms of AP | 16 (18%) | 11 (12%) | 10 (11%) |
| Exercise capacity (W) | 142 (30) | 142 (30) | 136 (26) |
| ≥0.1 mV ST-segment depression on exercise ECG | 20 (23%) | 23 (26%) | 19 (22%) |
| Randomization | | | |
| Placebo | 46 (52%) | 47 (53%) | 46 (52%) |
| Gemfibrozil | 42 (48%) | 42 (47%) | 42 (48%) |
| Cholesterol | | | |
| Total (mmol/L) | 5.1 (0.8) | 5.3 (0.6) | 5.2 (0.7) |
| LDL (mmol/L) | 3.7 (0.6) | 3.7 (0.5) | 3.7 (0.6) |
| HDL (mmol/L) | 0.79 (0.16) | 0.84 (0.15) | 0.81 (0.17) |
| Triglycerides (mmol/L) | 1.69 (0.72) | 1.68 (0.67) | 1.63 (0.67) |
| Glucose (mmol/L) | 4.9 (0.6) | 4.7 (0.7) | 4.6 (0.5)* |

AMI indicates acute myocardial infarction; AP, angina pectoris; BMI, body mass index; and CABB, coronary artery bypass surgery. Data are mean (SD) or n (% total).

*$P<0.05$ between lowest and highest tertiles of SDNN.

baseline SDNN and the change in the minimum luminal diameter of all the native vessels ($r=0.26$, $P<0.001$).

Twenty-four patients were found to have new coronary artery lesions in repeated coronary angiograms. There were no differences in HR or HR variability, ie, SDNN 110±26 versus 108±32 ms (not significant [NS]), between the patients with and without new stenoses.

## Comparison of Placebo and Gemfibrozil Groups

The relationship between the progression of focal coronary atherosclerosis and HR variability was observed only in the patients randomized to placebo treatment (Figure 2), but no significant relationship was observed in those receiving gemfibrozil therapy (Figure 3). Marked progression of focal atherosclerosis was observed mainly in the patients with the lowest SDNN in the placebo group, ie, decrease in the mean per-patient minimal luminal diameter of all native segments −0.17 mm (95% CI, −0.23 to −0.12 mm) in the lowest tertile, −0.05 mm (95% CI, −0.08 to −0.01 mm) in the middle tertile, and only −0.01 mm (95% CI, −0.04 to 0.02 mm) in the patients with highest HR variability ($P<0.001$ between the tertiles; Figure 2). A significant correlation was observed between the baseline SDNN and the change in the minimal luminal diameter of all native vessels ($r=0.44$, $P<0.001$) in the placebo group. In the gemfibrozil group, the per-patient change in the minimum luminal diameter was −0.03 mm (95% CI, −0.07 to 0.02 mm) in the lowest SDNN tertile, −0.07 mm (95% CI, −0.12 to −0.03 mm) in the middle tertile, and −0.05 mm (95% CI, −0.11 to 0.01 mm) in the highest tertile, respectively (NS; Figure 3); no correlation was observed between the SDNN and the change in the minimum luminal diameter ($r=0.08$, NS).

## Predictors of Progression of Coronary Atherosclerosis

The patients were also divided into tertiles according to the per-patient change in the minimum luminal diameter of all native-segment stenoses. Patients in the lowest tertile had a marked progression of focal atherosclerosis (decrease in the minimum luminal diameter −0.25±0.11 mm), minimal or no progression was observed in the middle tertile (−0.05±0.04 mm), and regression of focal atherosclerosis was observed in the highest tertile (0.10±0.07). The progression of discrete coronary stenoses was related to the time-domain measures of HR variability, also when normalized by reference to the averaged HR, and to all the spectral components of HR variability (Table 3). Minimum HR (during sleep) was also faster in the patients with marked progression of discrete stenoses than in those with minimal progression or regression, but the maximum HR (awake) did not differ between the groups.

**TABLE 2. Angiographic Data in Relation to Heart Rate Variability**

| | SDNN 31–90 ms (n=88) | SDNN 91–117 ms (n=89) | SDNN 118–250 ms (n=88) |
|---|---|---|---|
| All native segments | | | |
| Baseline MLD (mm) | 1.60±0.40 | 1.64±0.31 | 1.64±0.33 |
| Change in MLD (mm) | −0.107 (0.18) | −0.062 (0.14)* | −0.030 (0.14)† |
| Baseline ADS (mm) | 2.25±0.37 | 2.28±0.35 | 2.28±0.36 |
| Change in ADS (mm) | −0.033 (0.12) | −0.033 (0.10) | −0.014 (0.08) |
| Unaffected segments | | | |
| Baseline MLD (mm) | 1.65±0.55 | 1.68±0.50 | 1.69±0.53 |
| Change in MLD (mm) | −0.132 (0.21) | −0.073 (0.30) | −0.030 (0.21)† |
| Baseline ADS (mm) | 2.31±0.57 | 2.33±0.55 | 2.32±0.55 |
| Change in ADS (mm) | −0.036 (0.15) | −0.025 (0.17) | −0.016 (0.12) |
| Graft affected segments | | | |
| Baseline MLD (mm) | 1.62±0.53 | 1.63±0.44 | 1.64±0.55 |
| Change in MLD (mm) | −0.113 (0.30) | −0.071 (0.23) | −0.039 (0.25)‡ |
| Baseline ADS (mm) | 2.55±0.55 | 2.54±0.50 | 2.57±0.50 |
| Change in ADS (mm) | −0.064 (0.19) | −0.065 (0.22) | −0.036 (0.18) |
| Graft dependent segments | | | |
| Baseline MLD (mm) | 1.41±0.30 | 1.44±0.26 | 1.40±0.27 |
| Change in MLD (mm) | −0.036 (0.20) | −0.030 (0.18) | −0.006 (0.17) |
| Baseline ADS (mm) | 1.90±0.28 | 1.92±0.26 | 1.87±0.25 |
| Change in ADS (mm) | 0.001 (0.12) | −0.006 (0.14) | 0.016 (0.10) |
| Ejection fraction (%) | 69 (11) | 69 (10) | 69 (11) |

ADS indicates average diameter of segments; and MLD, minimal luminal diameter. Values are mean (SD).

*$P<0.05$ between the middle and lowest tertiles of SDNN.

†$P<0.01$ and ‡$P<0.05$ between the highest and lowest tertiles of SDNN.

In univariate analyses, the per-patient change in the minimum luminal diameters of the stenoses in all native vessels was related to SDNN ($P<0.0001$), triglyceride level ($P=0.009$), randomization to placebo or gemfibrozil ($P=0.003$), minimum HR ($P=0.02$), and to systolic and diastolic blood pressure ($P=0.02$ for both), but not to any other measured variable. In a multiple regression analysis, the change in the minimum luminal diameter was best predicted by the SDNN ($\beta=0.24$, $P=0.0001$) and triglyceride level ($\beta=-0.16$, $P=0.009$); no other variables entered the equation.

## Discussion

The main observation was that reduced HR variability, as analyzed from ambulatory ECG, predicted the progression of human coronary atherosclerosis. These data corroborate previous evidence on the significance of HR variability for clinical manifestations of coronary artery disease.[1–7] The association between low HR variability and the progression of coronary artery disease was not explained by common risk factors for atherosclerosis, or by the severity of ischemic heart disease at the time of analysis of HR variability, supporting the view that there may be an independent

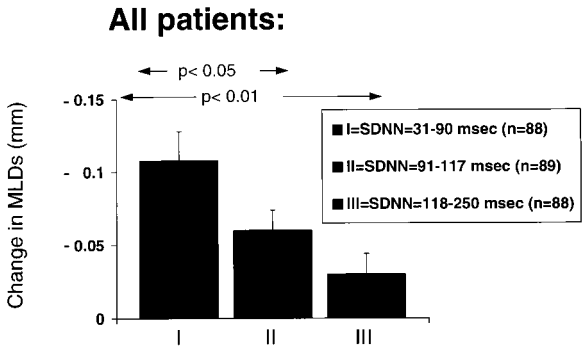


**Figure 1.** Per-patient changes in the MLD of stenoses in all native vessels of patients divided into tertiles according to the SDNN, measured in 12-hour electrocardiography. Values are mean±SEM.

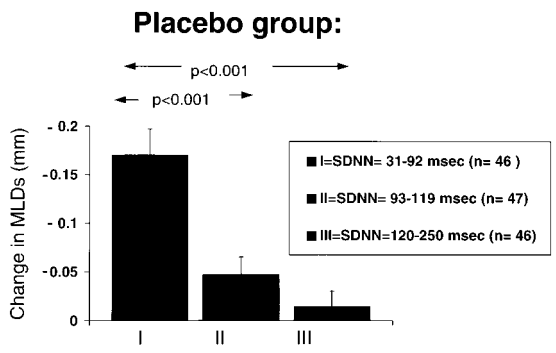


**Figure 2.** Per-patient changes in MLD of stenoses in all native vessels of patients randomized to placebo treatment and divided into tertiles according to the SDNN, measured in 12-hour electrocardiography. Values are mean±SEM.

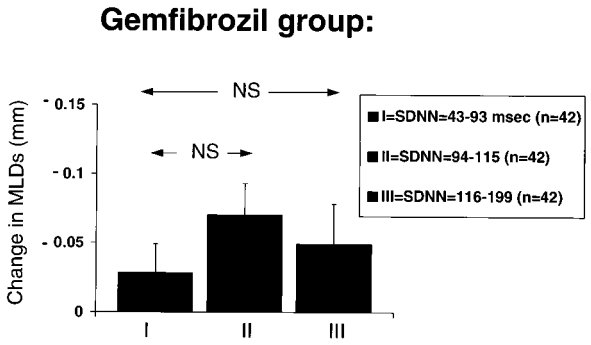


**Figure 3.** Per-patient changes in MLD of stenoses in all native vessels of patients randomized to gemfibrozil treatment and divided into tertiles according to the SDNN, measured in 12-hour electrocardiography. Values are mean±SEM.

relationship between HR variability and the progression of coronary atherosclerosis.

Despite the epidemiological evidence of an association between low HR variability and cardiovascular mortality,[5–7] the causes and mechanisms of this association have not been well known. Follow-up and case-control studies in patients after myocardial infarction have suggested that low HR variability predicts the occurrence of arrhythmic events,[24,25] but results in other populations suggest that reduced HR variability may also predict the occurrence of vascular events, such as angina pectoris, myocardial infarction, and coronary death.[7,23] The present observations give an insight into the pathophysiology, and mechanisms for the observed clinical associations, showing that reduced HR variability is related to accelerated progression of coronary atherosclerosis, rather than being a consequence of severe ischemic heart disease itself.

Elevated casual HR has been shown to predict cardiovascular mortality in a number of large-scale prospective epidemiological studies.[1–3] Ambulatory ECG recordings have shown that the minimum HR measured during a 24-hour period is even more closely related to cardiac events than the casual HR or 24-hour average HR,[26] and blunted circadian rhythm of autonomic modulation of HR has been described in patients with coronary artery disease.[22] In this study, the elevated minimum HR during sleeping hours, but not the maximum HR, was found to be related to the progression of coronary artery stenoses, also providing a possible explanation for the prior epidemiological and clinical observations.[1–3]

The observed associations between HR, HR variability, and progression of focal atherosclerosis may be explained by hemodynamic factors, effects of the autonomic nervous system, or a combination of these factors. The role of hemodynamic factors in the localized nature of coronary artery disease, ie, localization of coronary stenoses to specific proximal portions of the coronary arteries around the arterial branches, has been speculated upon in earlier studies, and it has been shown that hemodynamic factors may play an important role in the progression and regression of these lesions.[8,15] The present observations support the concepts of these experimental findings by showing that reduced HR variability, and elevated minimum HR, predicted the progression of discrete coronary stenoses located in the proximal portions of native coronary vessels, but not the progression of diffuse disease, or the development of new coronary lesions. The lack of association between HR variability and progression of diffuse atherosclerosis may be explained by different impacts of hemodynamic factors on progression of focal and diffuse atherosclerosis, and by the interaction between bypass grafts and local hemodynamics. Hemodynamically mediated mechanisms of atherosclerosis may be more closely related to geometric aspects of vulnerable areas, ie, discrete lesions proximal to bypass grafts but not distal diffuse disease, which promote eddy formation, low shear, and increased exposure to blood-born elements that are atherogenic. Abnormal baroreflex-mediated HR fluctuation and elevated HR have also been associated with increased arterial stiffness,[12,27] and frequency-dependent arterial stiffness may have influence on progression of atherosclerotic lesions.

**TABLE 3. Heart Rate Variability and Heart Rate in Relation to the Progression of Focal Coronary Atherosclerosis**

| | Change in MLD From −1.06 to −0.11 (n=88) | Change in MLD From −0.11 to 0.02 (n=89) | Change in MLD From 0.02 to 0.38 (n=88) |
|---|---|---|---|
| SDNN (ms) | 97±26 | 113±30† | 116±33‖ |
| SDNNi | 101±23 | 116±29† | 117±31§ |
| SDANN (ms) | 66±19 | 72±21 | 74±21§ |
| ULF power (ln) | 7.64±0.8 | 7.89±0.62* | 7.90±0.69‡ |
| VLF power (ln) | 6.99±0.68 | 7.15±0.77 | 7.23±0.65‡ |
| LF power (ln) | 5.78±0.82 | 5.93±0.76 | 6.07±0.81‡ |
| HF power (ln) | 4.90±0.70 | 5.09±0.75 | 5.20±0.67‡ |
| Min HR (bpm) | 52.3±6.8 | 51.4±6.8 | 49.7±5.9§ |
| Max HR (bpm) | 83.4±5.8 | 84.0±6.0 | 83.9±5.4 |
| Avg RR interval (ms) | 62.8±7.1 | 61.5±6.9 | 60.4±7.0‡ |

HF indicates high frequency; LF, low frequency; ln, logarithmic transformation; MLD, a per-patient change in minimal luminal diameter of all native vessels; SDANN, standard deviation of R-R intervals measured from 5-minute segments; SDNNi, standard deviation of all R-R intervals divided by average R-R interval; ULF, ultra-low frequency; and VLF, very-low frequency. Values are mean±SD.

*$P<0.05$ and †$P<0.01$ between the lowest and middle tertiles.

‡$P<0.05$, §$P<0.01$, and ‖$P<0.001$ between the lowest and highest tertiles.

The mechanism linking hemodynamic factors to the progression of discrete localized coronary lesions has been proposed to be the effects of blood flow dynamics on the arterial wall.[28] Movements of atherogenic particles over the endothelium, and vascular smooth cell proliferation, are affected by the fluid velocity and flow characteristics in the vicinity of the endothelium.[28,29] Recirculation and turbulence in the blood flow, and changes in shear stress, have been shown to result in morphological changes in the vascular endothelial cells and in intimal thickening, promoting accumulation of atherogenic particles within the endothelium.[15,29,30] Enhanced pulsatile flow has been observed to foster turbulence and recirculation,[31] and this has been proposed to be a mechanism whereby a fast HR accelerates the progression of discrete coronary stenoses in monkeys fed an atherogenic diet.[9] A combination of fast HR during sleep and enhanced de novo synthesis of lipid particles observed during sleeping hours[32] may accelerate the progression of human atherosclerosis. Loss or reduction of beat-to-beat variation in pulsatile flow, in addition to an elevated rate, may favor the localization of turbulence and recirculation to the same, specific anatomic segments of the arterial wall, further enhancing the atherosclerotic process in these localized areas.

The autonomic nervous system may also affect coronary atherosclerosis.[9,33] Reduced HR variability and elevated HR result from altered cardiac autonomic regulation with sympathetic predominance and/or reduced vagal tone. Increased sympathetic tone with elevated catecholamine levels may have direct effects on vascular smooth muscle cells,[34] or it may affect other factors promoting the progression of atherosclerosis.[35] The combined effects of HR variability on local fluid dynamics and the effects of autonomic nervous system may contribute to the observed progression of focal coronary atherosclerosis, but further investigations will be needed to elucidate the exact mechanisms.

The present observations cannot confirm any direct causal relationship between reduced HR variability and the progression of coronary artery disease because we cannot exclude the possibility that low HR variability may be an indicator of other factors, not measured here, in relation to the progression of atherosclerosis. It is possible, for example, that there may be a genetic link between HR variability and atherogenesis, independent of hemodynamics or the autonomic nervous system. The present observations may likewise not be applicable to other populations with different risk factors for atherosclerosis because only male patients with previous bypass surgery and a specific lipid abnormality were included. Of potential interest for future research is the role of impaired HR variability in other populations, eg, in diabetic subjects or patients with heart transplants, because both groups commonly experience rapid progression of atherosclerosis and reduced HR variability.

HR variability was the strongest independent predictor of the progression of focal coronary atherosclerosis in this population, and lipid-modifying therapy seemed to prevent progression mainly in the tertile of patients with the lowest HR variability. Whether recordings of long-term ambulatory ECG and measurement of HR variability will help in selecting patients for more aggressive antiatherogenic therapy merits further investigation.



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## References

1. Kannel WB, Kannel C, Paffenbarger RS, Cupples LA. Heart rate and cardiovascular mortality: The Framingham Study. *Am Heart J*. 1987;113: 1489–1494.
2. Gillum RF, Makuc DM, Feldman JJ. Pulse rate, coronary heart disease, and death: The NHANES I Epidemiological Follow-up Study. *Am Heart J*. 1991;121:172–177.
3. Mensink GBM, Hoffmeister H. The relationship between resting heart rate and all-cause, cardiovascular and cancer mortality. *Eur Heart J*. 1997;18:1404–1410.
4. Hjalmarson A, Gilpin EA, Kjekshus J, Schieman G, Nicord P, Henning H, Ross J Jr. Influence of heart rate on mortality after myocardial infarction. *Am J Cardiol*. 1990;65:547–551.
5. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ, and the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59:256–262.
6. Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky LM, Klieger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*. 1992;85:164–171.
7. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events: The Framingham Heart Study. *Circulation*. 1996;94:2850–2855.
8. Filipovsky J, Ducimetiere P, Safar ME. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. *Hypertension*. 1992;20:333–339.
9. Beere PA, Glagov S, Zarins CK. Retarding effect of lowered heart rate on coronary atherosclerosis. *Science*. 1984;226:180–182.
10. Kaplan JR, Manuck SB, Adams MR, Weingard KW, Clarkson TB. Inhibition of coronary atherosclerosis by propranolol on behaviorally predisposed monkeys fed an atherogenic diet. *Circulation*. 1987;86: 1364–1372.
11. Kaplan JR, Manuck SB, Clarkson TB. The influence of heart rate on coronary atherosclerosis. *J Cardiovasc Pharm*. 1987;10(suppl 2):S100–S102.
12. Sa Cunha R, Pannier B, Benetos A, Siche J-P, London GM, Mallion JM, Safar ME. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. *J Hypertension*. 1997;15: 1423–1430.
13. Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, Williams PT, Johnstone IM, Champagne MA, Krauss RM, Farquliar JW. Effects of intensive multiple risk factor reductions on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: The Stanford Coronary Risk Intervention Project. *Circulation*. 1994;89:975–990.
14. Gotto AM Jr. Lipid lowering, regression and coronary events: a review of the Interdisciplinary Council of Lipids and Cardiovascular Risk Intervention, Seventh Council Meeting. *Circulation*. 1995;92:646–656.
15. Schwartz CJ, Mitchell JRA. Observations on localization of arterial plaques. *Circ Res*. 1972;11:63–73.
16. Ip JH, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: role of vascular injury and smooth muscle cell proliferation. *J Am Coll Cardiol*. 1990;15:1667–1687.
17. Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. *Circ Res*. 1990;66: 1045–1066.
18. Hamsten A. Hemostatic function and coronary artery disease. *N Engl J Med*. 1995;332:677–678.
19. Frick MH, Syvänne M, Nieminen MS, Kauma H, Majahalme S, Virtanen V, Kesäniemi YA, Pasternack A, Taskinen M-R, for the Lopid Coronary Angiography Trial (LOCAT) Study Group. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. *Circulation*. 1997;96:2137–2143.
20. Syvänne M, Taskinen M-R, Nieminen MS, Manninen V, Kesäniemi YA, Pasternack A, Nawrocki JW, Haber H, Frick MH. A study to determine the response of coronary atherosclerosis to raising low HDL cholesterol with a fibric-acid derivative in men after coronary bypass surgery: the

rationale, design and baseline characteristics of the LOCAT study. *Control Clin Trials*. 1997;18:93–119.
21. Syvänne M, Nieminen MS, Frick MH. Accuracy and precision of quantitative arteriography in the evaluation of coronary artery disease after coronary bypass surgery: a validation study. *Int J Vasc Imaging*. 1994; 10:243–252.
22. Huikuri HV, Niemelä MJ, Ojala S, Rantala A, Ikäheimo MJ, Airaksinen KEJ. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease: effects of arousal and upright posture. *Circulation*. 1994;90:121–126.
23. Huikuri HV, Mäkikallio TH, Airaksinen KEJ, Seppänen T, Puukka, P, Räihä IJ, Sourander LB. Power law relationship of heart rate variability as a predictor of mortality in the elderly. *Circulation*. 1998;97:2031–2036.
24. Hartikainen JEK, Malik M, Staunton A, Poloniecki J, Camm AJ. Distinction between arrhythmic and nonarrhythmic death after acute myocardial infarction based on heart rate variability, signal-averaged electrocardiogram, ventricular arrhythmias and left ventricular ejection fraction. *J Am Coll Cardiol*. 1996;28:296–304.
25. Perkiömäki JS, Huikuri HV, Koistinen MJ, Mäkikallio T, Castellanos A, Myerburg RJ. Heart rate variability and dispersion of QT interval in patients with vulnerability to ventricular tachycardia and ventricular fibrillation after previous myocardial infarction. *J Am Coll Cardiol*. 1997;30:1331–1338.
26. Perski A, Olsson G, Laudon C, deFaire V, Theorell T, Hamsten A. Minimum heart rate and coronary atherosclerosis: independent relations to global severity and rate of progression of angiographic lesions in men with myocardial infarction at a young age. *Am Heart J*. 1992;123: 609–616.
27. Bergel DH, Brooks DE, MacDermott AJ, Robinson JL, Sleight P. Baroreceptor firing frequency and activation of carotid sinus vascular smooth muscle in dogs. *J Physiol*. 1978;275:37P–38P.
28. Caro CG, Fitz-Gerald JM, Schroter RC. Arterial wall shear and distribution of early atheroma in man. *Nature*. 1969;223:1159–1161.
29. Sprague EA, Steinbach BL, Nerem RM, Schwartz CJ. Influence of laminar steady-state fluid-imposed wall shear stress on the binding, internalization, and degradation of low-density lipoproteins by cultured arterial endothelium. *Circulation*. 1987;76:648–656.
30. Predel, HG, Yang Z, von Segesser L, Turina M, Bühler FR, Lüscher TF. Implications of pulsatile stretch on growth of saphenous vein and mammary artery smooth muscle. *Lancet*. 1992;340:878–879.
31. Yellin EL. Laminar-turbulent transition process in pulsatile flow. *Circ Res*. 1966;19:791–804.
32. Jones PJH, Schoeller DA. Evidence for diurnal periodicity in human cholesterol synthesis. *J Lipid Res*. 1990;31:667–673.
33. Kukreja RS, Datta BN, Chakra-Varti RN. Catecholamine-induced aggravation of aortic and coronary atherosclerosis in monkeys. *Atherosclerosis*. 1981;40:291–298.
34. Yu S-M, Tsai S-Y, Guh J-H, Ko F-N, Teng C-M, Ou J-T. Mechanisms of catecholamine-induced proliferation of vascular smooth muscle cells. *Circulation*. 1996;94:547–554.
35. Dzau VJ, Sarbs FM. Regulation of lipoprotein metabolism by adrenergic mechanisms. *J Cardiovasc Pharmacol*. 1987;10(suppl 9):S2–S6.

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