Diurnal heart rate reactivity: a predictor of severity of experimental coronary and carotid atherosclerosis

Hisham S. Bassiouney, Christopher K. Zarins, Daniel C. Lee, Christopher L. Skelly, John E. Fortunato and Seymour Glagov

**Background** Elevated awake resting heart rate (HR) has been shown to be a major risk factor for cardiovascular disease. Since coronary ischaemic events appear to peak during transition from sleep to awake HR, we sought to determine whether the degree of diurnal HR fluctuation (dHRV) is an independent predictor of coronary and peripheral atherogenesis. In this study, we varied both baseline HR and dHRV using sino-atrial node ablation (SNA) in a primate model of diet-induced atherogenesis and determined the degree of plaque formation relative to both HR parameters.

**Methods** HR was recorded continuously for 6 months by an implantable intraaortic sensor/transmitter in 17 active unrestrained male cynomolgus monkeys. In nine monkeys, SNA was employed to create a wide spectrum of dHRV, and the power amplitude of dHRV was determined for the daily HRV cycle with power spectral analysis. After a 6-month diet induction period, percent coronary and carotid stenosis, intimal thickness and area were quantitated in each animal.

**Results** Total serum cholesterol and mean HR were no different between high (n = 10) and low (n = 7) dHRV groups (866 mg% vs. 740 mg%, P = 0.2 and 130 ± 22 and 115 ± 13, P > 0.1, respectively). Percent carotid stenosis was markedly greater in both high HR and dHRV animals ([HR], 54 ± 19 vs. 35 ± 10, P < 0.04) and ([dHRV], 54 ± 17 vs. 32 ± 10, P < 0.01). Significant increases in all measures of coronary atherogenesis were found in high dHRV animals when compared with those with low dHRV (percent stenosis: 48% ± 22 vs. 23% ± 16, P < 0.02), lesion area: 1.2 ± 0.8 vs. 0.3 ± 0.3, P < 0.02), and (intimal thickness: 0.3 ± 0.1 vs. 0.1 ± 0.1, P < 0.01), respectively. While there was a trend towards greater coronary atherogenesis in animals with high HR, this did not reach statistical significance.

**Conclusion** Elevated HR and dHRV are both associated with enhanced experimental atherosclerotic plaque formation. However, a greater degree of carotid and coronary atherogenesis is observed in animals with high dHRV. These findings suggest that elevated dHRV is a stronger predictor for susceptibility to atherogenesis than elevated HR alone. Such a relationship may be attributed to the potential role of dHRV in modulating the frequency of adverse near wall haemodynamic forces, which have been shown to induce atherosclerotic plaques. Lowering of dHRV in humans by exercise or pharmacological agents may have a beneficial role in retarding atherosclerotic plaque induction, progression and complication. *J Cardiovasc Risk* 9:331–338 © 2002 Lippincott Williams & Wilkins.


Keywords: atherosclerosis, coronary artery, carotid artery, heart rate reactivity

Introduction

Several clinical and experimental studies have demonstrated that elevated heart rate (HR) is a predictor of increased cardiovascular morbidity and mortality [1–8]. An independent effect of HR on cardiovascular death has been shown in a number of epidemiological studies [4–8] such as the Framingham study [1]. Support for this association has also been borne out in nonhuman primate experiments where plaque formation was shown to correlate positively with HR; whereas, lowered HR retarded atherosclerosis both in the coronary circulation and at the carotid bifurcation [2,3]. It is therefore not surprising that clinical application of pharmacologic agents which lower HR (β-blockers and calcium channel blockers) reduce the incidence of secondary coronary events [9,10].

Recently, HR variability (HRV) in response to physical and psychological stresses has been identified as a potential risk factor for accelerated atherosclerosis [11–17]. Kaplan *et al.* [11,12,17] have shown that elevated HR reactivity to a standard stress challenge was associated with enhanced *in vivo* coronary artery plaque formation in both male and female cynomolgus monkeys. This was independent of baseline HR, blood pressure and lipid profile. Individuals with heightened cardiac reactivity also appear to be at higher risk for the
development of cardiovascular disease. For example, retrospective studies have identified Type A behaviour patterns as predictive of greater coronary atherosclerosis and related coronary events [13].

The observation that acute myocardial infarction and sudden cardiac death are more frequent in the morning has raised considerable interest in nycthemeral fluctuation of HR. The objective of this study was to investigate the significance of resting HR and its reactivity as independent variables for experimental coronary and carotid atherosclerotic plaque formation. Resting HR and its variability was assessed in unrestricted caged male cynomolgus monkeys in which SNA was used to lower baseline HR and dampen its variability, thereby creating a wide spectrum of HR and HRV in the animals studied. After 6 months of diet-induced atherogenesis, coronary and carotid atherosclerosis was quantitated and compared in animal subgroups with different baseline HR and HRV. In this investigation, diurnal HRV was selected as the measure of circadian alterations in the HR frequency imposed by psychological and physiological stimuli during the sleep–wake cycle transition.

**Methods**

**Animal model and diet**

Seventeen adult male cynomolgus monkeys (*Macaca fascicularis*) were selected for this study. Housing and handling of animals was in compliance with ‘Principles of Laboratory Animal Care’ and ‘Guide for the Care and Use of Laboratory Animals’ (National Institutes of Health, publication No.80-23, revised 1985). Nine monkeys were randomly assigned to undergo SNA to decrease the HR and HRV. SNA involved electrocautery of the *crista terminalis* at the entry of the superior vena cava into the right atrium and suture of the resulting defect. Five days after SNA, all 17 animals were fed an atherogenic diet containing 2% cholesterol and 25% peanut oil for 6 months [18]. Serum lipids including total cholesterol, triglycerides, HDL and LDL were measured on a bi-weekly basis in all animals.

**Blood pressure and heart rate telemetry**

HR and blood pressure (BP) (including systolic, diastolic and mean blood pressure) were monitored using a 24-h radio-telemetry system (Data Sciences, Inc., St Paul, MN, USA) in the unrestricted animals. The system consisted of (1) a small battery powered transmitter, (2) an intraaortic pressure sensor, (3) a telemetry receiver located near the cage and (4) a PC-based data acquisition system which converts telemetry pressure to HR (Figure 1). Each animal was continuously monitored for a period of 10 weeks (1 week prior to and 9 weeks after diet induction). Telemetry data were recorded for a period of 1 min every 20 min during the 10-week period.

**Power spectral analysis of heart rate variability**

The HR data series of each animal was analysed using power spectral analysis (Dataquest Analysis Module, Data Sciences, Inc., St Paul, MN, USA) to determine dHRV. dHRV represents the degree of HR variance at the ‘ultra low frequency power’ or one cycle per day. Fourier transformation was utilized to partition the total variance of the heart rate into variances with their corresponding frequency. A plot of absolute power in μvolts/hertz² (μV Hz²) versus frequency was then generated from the computations. Fourier transformation of the HR series at 20-min intervals yields a consistent power peak at 11.5 μHz (which corresponds to 24 h per cycle of HR variation). This power amplitude in μV/Hz² was measured and defined as diurnal heart rate (dHRV; Figure 2).

**Quantification of coronary and carotid atherosclerosis**

After 6 months of atherogenic diet, animals were sacrificed using intravenous administration of an overdose of sodium pentobarbital. The heart and arterial tree were pressure perfusion fixed *in situ* at 100 mmHg for 1 h by iliofemoral infusion of 3% glutaraldehyde [19]. Eight samples of the coronary tree, including sections from the left main, left anterior descending (proximal, middle and distal portion), right and circumflex were removed as complete transverse rings at standard sites from each animal [20]. Both the right

![Fig. 1](image-url)
and left common carotid arteries and their internal and external branches were removed from each animal. Five sections of the left and right distal common, bifurcation and proximal internal carotid arteries were obtained (Figure 3). Each cut segment of the carotid and coronary artery was embedded in paraffin and 5-μm thick sections from each block were stained with Weigert von Gieson connective tissue stain. Atherosclerotic plaque area in each section was quantified by means of a contour tracing system using a Hewlett Packard digitizer (Hewlett Packard Co., Medical Products, Andover, MA, USA) interfaced with a mini-computer and a Palmer-Leitz projecting microscope (Palmer-Leitz, Germany). Contours of the lumen, internal elastic lamina (IEL), an outer limit of the media or external elastic lamina were traced. Lesion area was defined as the difference between the area circumscribed by the IEL and the area of the lumen. The mean radial thickness was averaged from several radial intersects. Percent stenosis was calculated using the equation: lesion area/IEL × 100.

Atherosclerotic plaque burden
Significant stenosis was defined as 25% or greater lumen stenosis. The number of coronary sections (10 per animal) with 25% stenosis or more was determined as was the number of carotid (eight per animal) sections with 25% stenosis or more. The percentage of coronary and carotid sections with significant stenosis for each animal was defined as the carotid or coronary atherosclerotic burden. The atherosclerotic plaque burden for HHR and LHR as well as HHRV and LHRV animals was then determined using the odds ratio.

Statistical analysis
Results were expressed as mean ± standard deviation (SD), while the dependent variables included carotid and coronary percent stenosis, lesion area and mean intimal thickness. The independent variables included both haemodynamic parameters (HR, dHRV, and BP) and serum lipids. For comparisons between mean values, paired t-tests were utilized and 95% confidence intervals calculated. Differences were considered to be significant if P was less than 0.05.

Results
Heart rate (HR)
Mean heart rate (HR) for all 17 animals before and after atherogenic diet was 131 ± 19 (range 106–172) and 124 ± 20 (range 98–173) respectively. Animals were divided into high heart rate (HHR) and low heart rate (LHR) groups about the mean HR of the entire group of animals after diet induction. Mean HR of the LHR group (n = 8) was 109 ± 7, and of the HHR group (n = 9) was 139 ± 17 (P < 0.001). Of the nine animals subjected to SNA, HR was reduced in five from 137 ± 14 to 111 ± 11 (P < 0.01). In the remaining four, HR was not significantly changed.
Heart rate variability
As described previously in the methods section 1, dHRV was represented by the power amplitude at the frequency of 11.5 μHz (cycle of HR variation occurring every 24 h) (Figure 4). Mean dHRV for all animals before diet was 27.3 ± 9.8 μV/Hz² (range 12.5–46 μV/Hz²) and after diet modification was 26.3 ± 10.3 μV/Hz² (range 7.6–42.4 μV/Hz²). SNA successfully reduced dHRV from 27.7 ± 3.5 to 19.3 ± 6 μV/Hz² (P < 0.04) in four out of nine animals. Animals were divided into high HRV (HHRV) and low HRV (LHRV) groups about the mean dHRV of the entire group of animals after diet induction. Mean dHRV of the LHRV group (n = 7) was 16.4 ± 5.3 μV/Hz², and of the HHRV group (n = 10) was 33.2 ± 6.3 μV/Hz² (P < 0.0001).

Blood pressure
Blood pressure (BP) of the entire group of animals before atherogenic diet was 117 ± 15/75 ± 16 (range 76–158/46–128) mmHg with a mean BP of 95 ± 17 (range 60–112) mmHg and was not changed after diet induction [119 ± 21/75 ± 28 (range 87–158/44–128) mmHg, a mean BP of 93 ± 25 (range 60–112) mmHg]. These parameters were not altered subsequent to SNA (P > 0.6) (Table 1). There was no difference in BP between LHR and HHR groups as well as between LHRV and HHRV groups (Table 1).

Serum lipids (mg/dl)
Mean plasma cholesterol increased from 111 ± 28 (range 46–147) to 814 ± 227 (range 346 to 1259) after 6 months of atherogenic diet (P < 1 × 10⁻⁵). Atherogenic diet also resulted in significant increases in plasma triglycerides and LDL from 49 ± 14 to 85 ± 63, P < 0.05, and from 40 ± 18 to 776 ± 230, P < 1 × 10⁻⁸) (Table 2).

Plaque formation in relation to HR and HRV
Mean percent carotid stenosis at the bifurcation region and at the most stenotic section for all 17 animals after diet intervention was 45% ± 18 and 47% ± 18 (range 18–76%), respectively. The region of the carotid bifurcation exhibited the greatest degree of plaque burden. Mean lesion area at the bifurcation for all animals was 2.39 ± 1.1 mm² (range 0.88–4.5 mm²). Due to the irregularity of contour in the majority of specimens at the bifurcation region, the calculated mean intimal thickness was not reliable and was excluded in the analysis. For the coronary arteries, mean intimal thickness, percent stenosis, and lesion area of the most occlusive lesion in all 17 monkeys after the atherogenic diet were 0.2 ± 0.14 (range 0–0.42) mm, 38 ± 23% (range 0–79%), and 0.82 ± 0.78 mm² (range 0–2.5 mm²), respectively.

Comparisons for carotid and coronary plaque formation between HHR and LHR groups are presented in

Table 1. Comparisons of BP before and after SNA, for LHR and HHR animals, and for LHRV and HHRV animals. Results are mean ± SD, in mmHg

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Mean BP</th>
</tr>
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<tbody>
<tr>
<td>Before surgery</td>
<td>117 ± 18</td>
<td>75 ± 16</td>
<td>95 ± 17</td>
</tr>
<tr>
<td>After surgery</td>
<td>119 ± 21</td>
<td>75 ± 28</td>
<td>93 ± 25</td>
</tr>
<tr>
<td>P-value</td>
<td>&gt; 0.6</td>
<td>&gt; 0.9</td>
<td>&gt; 0.7</td>
</tr>
<tr>
<td>LHR (n = 8)</td>
<td>114 ± 23</td>
<td>72 ± 27</td>
<td>90 ± 26</td>
</tr>
<tr>
<td>P-value</td>
<td>&gt; 0.5</td>
<td>&gt; 0.6</td>
<td>&gt; 0.5</td>
</tr>
<tr>
<td>HHR (n = 9)</td>
<td>120 ± 15</td>
<td>78 ± 17</td>
<td>98 ± 15</td>
</tr>
<tr>
<td>P-value</td>
<td>&gt; 0.6</td>
<td>&gt; 0.6</td>
<td>&gt; 0.5</td>
</tr>
<tr>
<td>LHRV (n = 7)</td>
<td>115 ± 25</td>
<td>77 ± 29</td>
<td>93 ± 28</td>
</tr>
<tr>
<td>P-value</td>
<td>&gt; 0.6</td>
<td>&gt; 0.7</td>
<td>&gt; 0.8</td>
</tr>
</tbody>
</table>

Table 2. Effect of atherogenic diet on plasma lipids. Results are mean ± SD, in mg/dl

<table>
<thead>
<tr>
<th></th>
<th>Before diet</th>
<th>After diet</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>111 ± 28</td>
<td>814 ± 227</td>
<td>&lt; 1 × 10⁻⁵</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>49 ± 14</td>
<td>85 ± 63</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>40 ± 18</td>
<td>776 ± 230</td>
<td>&lt; 1 × 10⁻⁸</td>
</tr>
<tr>
<td>HDL</td>
<td>70 ± 6</td>
<td>30 ± 11</td>
<td>&lt; 1 × 10⁻¹⁰</td>
</tr>
</tbody>
</table>
Table 3. Comparison of atherogenesis for the carotid (A) and coronary arteries (B) in low and high HR animals. Results are mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>LHR (n = 8)</th>
<th>HHR (n = 9)</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Carotid atherogenesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Carotid stenosis closest to bifurcation</td>
<td>35 ± 10</td>
<td>54 ± 19</td>
<td>&lt; 0.04</td>
<td>(3.35)</td>
</tr>
<tr>
<td>% Carotid stenosis in most occlusive lesion</td>
<td>37 ± 12</td>
<td>55 ± 19</td>
<td>&lt; 0.05</td>
<td>(1.3, 34.7)</td>
</tr>
<tr>
<td>Carotid lesion area (mm²)</td>
<td>1.67 ± 0.79</td>
<td>3.01 ± 1</td>
<td>&lt; 0.02</td>
<td>(0.4, 2.3)</td>
</tr>
<tr>
<td>B. Coronary atherogenesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most occlusive coronary lesion</td>
<td>LHR (n = 8)</td>
<td>HHR (n = 9)</td>
<td>P-value</td>
<td>95% CI</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>27 ± 27</td>
<td>67 ± 16</td>
<td>&gt; 0.1</td>
<td>(-2.61, 42.6)</td>
</tr>
<tr>
<td>Lesion area (mm²)</td>
<td>0.56 ± 0.71</td>
<td>1.06 ± 0.8</td>
<td>&gt; 0.15</td>
<td>(-0.29, 1.27)</td>
</tr>
<tr>
<td>Intimal thickness (mm)</td>
<td>10.16 ± 0.16</td>
<td>0.23 ± 0.12</td>
<td>&gt; 0.3</td>
<td>(-0.08, 0.22)</td>
</tr>
</tbody>
</table>

Carotid stenosis was 1.5 times greater in HHR monkeys (for both specimens closest to the bifurcation and the most stenotic specimen) (P < 0.04, 95% CI [3.35] and P < 0.05 95% CI [1.3,34.7], respectively). Additionally, carotid lesion area was two times greater than LHR animals (P < 0.02, 95% CI [0.4,2.3]). Although atherosclerotic burden in the coronary arteries was not significantly different between HHR and LHR animals in spite of significantly lower HDL levels (P < 0.05) and almost two times greater LDL/HDL ratios (P < 0.01) compared with the LHR group, there was a trend towards greater plaque formation in HHR animals. Diurnal HRV was not significantly different between the two groups (P > 0.07) (Table 4).

Comparisons of carotid and coronary atherosclerosis between HHVR and LHRV groups are shown in Table 5. Plaque formation was significantly greater in HHVR versus LHRV animals for all parameters studied (P < 0.03). The degree of stenosis in both carotids and coronary arteries was two times greater in the HHVR group when compared with the LHRV group (for carotid specimens closest to the bifurcation, P < 0.01, 95% CI [6.7,37.3]; for the most stenotic carotid specimen, P < 0.03, 95% CI [4.4, 35.6]; for coronary lesions, P < 0.02, 95% CI [4.2, 45.8]). HHVR animals had about two times greater carotid lesion area (P < 0.01, 95% CI [0.4, 2.3]), and four times greater coronary lesion area (P < 0.02, 95% CI [0.2,1.5]) when compared with LHRV animals. Neither the serum lipids (i.e. total cholesterol, triglycerides, LDL, HDL, and LDL/HDL ratio) nor the mean HR were different between these two groups (P > 0.1) (Table 6).

Atherosclerotic plaque burden
To assess atherosclerotic plaque burden in the high and low HR and HRV animals, the percent of carotid and coronary arterial sections per animal with at least 25% luminal stenosis were determined using odds ratios. In the coronary segments HHHR animals had a risk of developing atherosclerosis 2.3 times that of LHR animals. High HR monkeys had a risk 5.8 times greater than those with LHRV. For the carotid segments, HHR and HHVR had a relative risk of 1.6 and 2.5 respectively, compared with LHR and LHRV (Table 7).

Table 4. Comparison of serum lipids and dHRV in LHR and HHR animals

<table>
<thead>
<tr>
<th></th>
<th>LHR (n = 8)</th>
<th>HHR (n = 9)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Serum lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>728 ± 211</td>
<td>890 ± 223</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>87 ± 72</td>
<td>73 ± 54</td>
<td>&gt; 0.6</td>
</tr>
<tr>
<td>LDL</td>
<td>684 ± 200</td>
<td>847 ± 216</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td>HDL</td>
<td>35 ± 13</td>
<td>24 ± 3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>21 ± 8</td>
<td>36 ± 10</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean dHRV (μV/Hz²)</td>
<td>22 ± 1</td>
<td>30 ± 9</td>
<td>&gt; 0.07</td>
</tr>
</tbody>
</table>

Results in mean ± SD.

Results are mean ± SD.

Table 5. Comparison of atherogenesis for the carotid (A) and coronary arteries (B) in low and high dHRV animals

<table>
<thead>
<tr>
<th></th>
<th>LHR (n = 7)</th>
<th>HHR (n = 10)</th>
<th>P-value</th>
<th>95% CI</th>
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<tr>
<td>A. Carotid atherogenesis</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>% Carotid stenosis closest to bifurcation</td>
<td>32 ± 10</td>
<td>54 ± 17</td>
<td>&lt; 0.014</td>
<td>(6.7, 37.3)</td>
</tr>
<tr>
<td>% Carotid stenosis in most occlusive lesion</td>
<td>35 ± 13</td>
<td>55 ± 16</td>
<td>&lt; 0.03</td>
<td>(4.38, 35.6)</td>
</tr>
<tr>
<td>Carotid lesion area (mm²)</td>
<td>1.58 ± 0.66</td>
<td>2.92 ± 1.04</td>
<td>&lt; 0.01</td>
<td>(0.39, 2.29)</td>
</tr>
<tr>
<td>B. Coronary atherogenesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most occlusive coronary lesion</td>
<td>LHR (n = 7)</td>
<td>HHR (n = 10)</td>
<td>P-value</td>
<td>95% CI</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>23 ± 16</td>
<td>48 ± 22</td>
<td>&lt; 0.02</td>
<td>(4.18, 45.82)</td>
</tr>
<tr>
<td>Lesion area (mm²)</td>
<td>0.33 ± 0.26</td>
<td>1.17 ± 0.8</td>
<td>&lt; 0.02</td>
<td>(0.17, 1.51)</td>
</tr>
<tr>
<td>Intimal thickness (mm)</td>
<td>0.1 ± 0.08</td>
<td>0.27 ± 0.14</td>
<td>&lt; 0.01</td>
<td>(0.04, 0.3)</td>
</tr>
</tbody>
</table>
more likely to have more advanced coronary and peripheral atherosclerotic lesions, which are more susceptible to disruption.

Although pharmacologic methods of reducing HR and dHRV using β-blockers and calcium channel blockers exist, we believe that their side effects may add confounding factors to our objective of isolating HR and dHRV as independent risk factors for atherogenesis. β-Blockers are known to cause elevation in plasma triglycerides [35], and calcium channel blockers may cause excessive peripheral vasodilatation, which leads to tachycardia [36]. SNA, on the other hand, decreases HR and dHRV without the added complicating side effects. Hence, this was the method selected for creating a greater spectrum of HR and HRV.

Our previous work using an identical primate model has shown that lowered HR was associated with less atherogenesis [2,3]. However, subsequent effort in fixed regulation of primate HR by extrinsic pacer did not reveal the expected positive relationship between HR and atherogenesis [28]. These data raised questions regarding the hypothesis that HR alone, by influencing flow pattern, velocity and wall shear stress [27,37], was the predominant mechanism affecting plaque formation and suggested the possibility that intrinsically regulated cardiac reactivity and HRV may play a role in atherogenesis. One proposed mechanism involved the effects of enhanced sympathoadrenal activation in hyperactive individuals which included unfavourable lipid metabolism and increased secretion and aggregation of platelets [13,38]. More recently, it has been suggested that regional susceptibility to atherosclerosis may correlate with increased endothelial permeability to molecules such as low-density lipoproteins [38,39]. Periodic fluctuation of haemodynamic shear forces near the endothelial surface may play a role in altered endothelial permeability to atherogenic particles. Another possible explanation is that HR and dHRV are merely markers of physical conditioning and the ability of individuals to respond favourably to psychological stressors.

The relationship between HRV and atherogenesis has not been previously demonstrated. Data from this study should lead to further studies into the role of other frequency bands (i.e. high, mid and low frequency powers) of HRV in plaque development and complication. Design of clinical studies involving comparison of HRV obtained from Holter monitor recordings and atherosclerotic plaque progression and complication is also warranted.

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5. Weihe S, Macdermott M, Mittleman M, Arntz H, Muller J. Sudden cardiac death is at increased risk for a role in triggering in a causal mechanism. Circulation 1993; 87: 1442–1450
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