Early autonomic malfunction in normotensive individuals with a genetic predisposition to essential hypertension

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Davrath, L. R., Y. Goren, I. Pinhas, E. Toledo, and S. Akselrod. Early autonomic malfunction in normotensive individuals with a genetic predisposition to essential hypertension. *Am J Physiol Heart Circ Physiol* 285: H1697–H1704, 2003.—One of the primary pathologies associated with hypertension is a complex autonomic dysfunction with evidence of sympathetic hyperactivity and/or vagal withdrawal. We investigated the possibility for early detection of essential hypertension on the basis of the analysis of heart rate (HR) and blood pressure fluctuations, which reflect autonomic control. Young adult normotensive offspring of one hypertensive parent (KHT; n = 12) and normotensive offspring of two hypertensive parents (YN; n = 14) participated in this study. ECG, continuous blood pressure, and respiration were recorded during steady-state conditions and under various autonomic challenges. Time-frequency decomposition of these signals was performed with the use of a continuous wavelet transform. The transform enables the extension of typical HR variability analysis to non-steady-state conditions. This time-dependent spectral analysis of HR allows time-dependent quantification of different spectral components reflecting the sympathetic and parasympathetic activity during rapid transitions, such as an active change in posture (CP). During an active CP from the supine to standing position, KHT demonstrated a significantly greater increase in the low-frequency fluctuations in HR than YN, indicating enhanced sympathetic involvement in the HR response to CP, and a reduced α-index, indicating decreased baroreceptor sensitivity. On recovery from handgrip, vagal reactivation was more sluggish in KHT. These results indicate the early existence of malfunctions in both branches of autonomic control in individuals at increased risk of hypertension. 

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Early autonomic malfunction in normotensive individuals with a genetic predisposition to essential hypertension.

ESSENTIAL HYPERTENSION is characterized by an increase in sympathetic nervous system (SNS) activity (13, 19), reduced vagal modulation of the sinoatrial (SA) node (14) and blunted baroreflex gain (24). Several studies utilizing invasive techniques such as muscle sympathetic nervous activity (MSNA) recordings (22) and measurements of norepinephrine spillover (10) have shown that augmented peripheral sympathetic activity is discernable in normotensive subjects with a family history of hypertension. To the best of our knowledge, no studies have been performed with the use of noninvasive techniques to examine autonomic control in normotensive subjects with a family history of hypertension. If autonomic differences can be detected before any elevation in blood pressure (BP) occurs, elucidation of these differences may lead to the design of a scheme for the noninvasive early detection of hypertension.

Heart rate (HR) variability (HRV) depends on the continuous interplay between spontaneous nervous input to the SA node, sympathetic and vagal efferent nerve activity, and the humoral milieu (17, 18). The instantaneous cardiovascular fluctuations express themselves in two main frequency regions: a high-frequency (HF) peak, located around the respiratory frequency, typically between 0.15 and 0.4 Hz, reflecting primarily vagal activity (HFHR) (1), and HF content of peripheral BP (HFBP) reflecting mechanical activity of respiration, and a low-frequency (LF) peak centered at ~0.1 Hz. The LF content of HR (LFRH) fluctuations is an estimate of combined vagal and β-sympathetic activity (7), whereas the LF content of peripheral BP (LFBP) fluctuations is an estimate of α-sympathetic activity (24).

Previous investigations (2, 4, 14, 18) using spectral analysis of HR and BP fluctuations have led to detection of autonomic alterations in hypertensive and mildly hypertensive patients in agreement with the well-known physiological changes occurring with hypertension. Studies have shown a progressive increase in LFHR (indicating increased central sympathetic activity) and reduced HFHR relative power of HRV with increasing severity of hypertension, as well as a reduced responsiveness to standing up, and a reduced α-index, in keeping with the well-known impairment in baroreflex gain (23). Vagal withdrawal has been correlated with the reduced HFHR fluctuations in hypertensives (14). In addition, sympathetic enhancement in mild hypertension was reflected by increased LFBP fluctuations at baseline compared with normotensives (2, 4), with a severely reduced response of LFBP fluctuations to the transition to standing in both mild hypertensives (2) and hypertensives (23).

Evaluation of non-steady-state conditions, such as those resulting when autonomic perturbations are applied, such as active change of posture (CP) and isometric handgrip (HG), requires the use of a time-
frequency approach for analysis, performed here with a dedicated continuous wavelet transform algorithm (30). This time-frequency decomposition provides traditional LF and HF frequency information as a function of time, thus allowing the examination of instantaneous changes in cardiovascular control.

Our main goal in this study was to evaluate autonomic control by means of real-time, noninvasive analysis of the spontaneous fluctuations in cardiovascular signals in young, adult, normotensive offspring of one essential hypertensive parent. Although these individuals are at increased likelihood to develop essential hypertension [genetic component of essential hypertension as high as 60% (21)], they are entirely normotensive, so discernable differences in the resting state are unlikely. Because we did not expect to find differences in the resting state, the experimental protocol included two autonomic challenges: CP and 30% maximal voluntary contraction (MVC) isometric HG. These autonomic perturbations were utilized in an attempt to unveil malfunctions in autonomic control indicative of impending hypertension.

METHODS

Subjects. Two groups of young age- and sex-matched normotensive subjects were studied. Individuals with one hypertensive parent were categorized as “KHT,” whereas subjects with two normotensive parents were designated as “YN.” There were no significant differences in anthropometric parameters between the groups. The KHT group included the following criteria: n = 12 (5 women and 7 men), age 29.8 ± 4.3 yr, body mass index (BMI) 24.1 ± 2.0 kg/m², waist-to-hip ratio 0.81 ± 0.11, and percent fat 22 ± 5%. The YN group included the following criteria: n = 14 (7 women and 7 men), age 28.7 ± 3.7 yr, BMI 23.2 ± 4.3 kg/m², waist-to-hip ratio 0.82 ± 0.08, and percent fat 19.8 ± 11%.

The Institutional Review Board of Tel Aviv University approved this noninvasive study, and all subjects signed a written informed consent form. This work fully conforms to the guidelines for research involving animals and human beings of the American Physiological Society. Before participation, they were screened with standard health history and physical activity questionnaires. All subjects were sedentary nonsmokers, and individuals with known autonomic disorders were excluded. Fifteen subjects were recorded in the YN group and fourteen in the KHT experimental group. Two KHT and one YN subject were removed from the analysis due to very slow breathing, which caused the HFHR region to merge with the LFHR region, making identification of the power in each frequency band unreliable.

Experimental procedures. Subjects reported to the laboratory between 8 AM and 9:30 AM, after consuming a light standard breakfast 1 h before arrival. Subjects abstained from the use of caffeine and other stimulants for 12 h before the study and strenuous exercise for 24 h before the study (11). Room temperature was controlled at 22–24°C. Subjects were requested to empty their bladder before beginning the test to avoid any increase of sympathetic nerve activity through bladder distention (9). Body weight was determined to the nearest 0.1 kg with the use of a balance scale (Detecto; Webb City, MO), and height (in cm) (shoeless) was measured by using the stadiometer on the scale. Skinfold thickness measurements were obtained at three sites (chest, abdomen, and thigh in men; subscapular, suprailliac, and thigh in women) using calipers (Lange, Cambridge Scientific Industries; Cambridge, MA). Waist circumference was measured (in cm) at the level of the umbilicus, and hip circumference was measured at the level of the symphysis pubis in front and at the maximal protrusion of the buttocks in the back with the use of a measuring tape.

Continuous, noninvasive finger arterial BP was measured with the use of a volume-clamp method with a hydrostatic height-correction system (Portapres, TNO Institute of Applied Physics Biomedical Instrumentation). Beat-to-beat R-R intervals were obtained from the continuous ECG signal. Resting BP was manually assessed over the brachial artery with a sphygmomanometer twice during the supine rest, before the experiment was begun and periodically throughout the experiment. The respiratory signal was measured with the use of the Respitrace rib and abdomen impedance belts. Voltage signals of the rib and abdomen were calibrated to tidal volume using an 800-ml spirobag, which the subject completely filled and emptied seven times, according to the manufacturer’s instructions. Patwardhan et al. (26) have shown that the act of voluntary control of breathing in and of itself alters autonomic balance in cardiovascular regulation.

In addition, because autonomic maneuvers utilized in this study required the subject’s active participation, we chose to use spontaneous breathing rate and depth.

Before the beginning of the experiment, each subject performed two brief (~5 s) maximal isometric contractions to determine his or her MVC strength with the use of an HG dynamometer (model TSD121C, Biopac). Thirty percent MVC was calculated from the highest maximal value. A discrepancy of >1 kg initiated another maximal HG attempt. The absolute force output from a HG dynamometer was displayed to the subjects on a computer monitor with the target force in the center of the screen. Each subject practiced performing 30% MVC with the nondominant hand by using visual feedback from the computer. Fatigue was used as the end point to standardize performance and perception of effort (29). Subjects were instructed to avoid breath holding and to maintain the rest of the body relaxed in the supine position during the HG. Subjects also practiced transitioning to stand within 5 s and performed the Valsalva maneuver for 15 s at an expiratory pressure of 40 mmHg. Results from the Valsalva maneuver and mental stress are reported elsewhere.

Experimental protocol. The experimental protocol consisted of the following steps: 1) 30 min of quiet supine rest (manual BP after 8 min, final 20 min used to determine steady-state HRV parameters); 2) the Valsalva maneuver: 40 mmHg expiratory pressure held for 15 s (2 trials, 5-min rest between each trial); 3) 7-min supine rest (manual BP after 2 min); 4) 3-min mental arithmetic with aloud reporting; 5) 7-min supine rest (manual BP after 2 min); 6) 30% MVC isometric HG held to exhaustion; 7) 10-min supine rest; and 8) active CP from supine to standing (5 s); and 9) the 5-min stand test.

Signal acquisition. The following signals were continuously monitored and simultaneously sampled at a sampling rate of 500 Hz using a multichannel device with Acknowledge software (model MP100, Biopac) and saved to a personal computer for off-line analysis: 1) ECG (leads II, V5) with the use of a Biopac System ECG 100B preamplifier; 2) continuous, noninvasive BP with the use of the Portapres TNO device; 3) respiration signal recorded over the rib and abdomen with a Respitrace pneumoplethysmograph; and 4) HG force with the use of an amplifier and dynamometer (model DA100B, Biopac).

Signal preprocessing. Calibration interruptions in the continuous BP signal were corrected with an algorithm devel-
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Table 1. Rest, CP, and HG-induced changes in R-R interval and BP variabilities

<table>
<thead>
<tr>
<th></th>
<th>LF norm</th>
<th>LF</th>
<th>HF norm</th>
<th>HF</th>
<th>LF/HF</th>
<th>(\alpha_{norm})</th>
<th>(\alpha)</th>
<th>LF BP</th>
<th>LF BP norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>KHT</td>
<td>2.67 ± 2.11</td>
<td>1.0</td>
<td>3.48 ± 5.52</td>
<td>1.0</td>
<td>1.70 ± 1.14</td>
<td>1.0</td>
<td>0.89 ± 0.37</td>
<td>3.35 ± 1.58</td>
</tr>
<tr>
<td></td>
<td>YN</td>
<td>4.26 ± 3.15</td>
<td>1.0</td>
<td>3.44 ± 4.25</td>
<td>1.0</td>
<td>1.95 ± 1.35</td>
<td>1.0</td>
<td>0.97 ± 0.25</td>
<td>4.02 ± 1.85</td>
</tr>
<tr>
<td>Immediate stand (15 s)</td>
<td>KHT</td>
<td>21.14 ± 11.92†</td>
<td>11.8 ± 11.2†</td>
<td>3.03 ± 2.81</td>
<td>3.60 ± 4.12</td>
<td>8.85 ± 5.89</td>
<td>0.82 ± 0.36†</td>
<td>0.67 ± 0.23†</td>
<td>47.86 ± 15.4</td>
</tr>
<tr>
<td></td>
<td>YN</td>
<td>13.14 ± 6.28</td>
<td>5.00 ± 6.4</td>
<td>2.71 ± 2.72</td>
<td>1.97 ± 3.04</td>
<td>9.03 ± 7.01</td>
<td>0.56 ± 0.19*</td>
<td>0.54 ± 0.15</td>
<td>49.31 ± 29.5</td>
</tr>
<tr>
<td>30-s Stand</td>
<td>KHT</td>
<td>23.60 ± 14.93*</td>
<td>12.8 ± 11.3*</td>
<td>4.39 ± 3.72</td>
<td>3.92 ± 3.78</td>
<td>6.98 ± 3.79</td>
<td>0.89 ± 0.38*</td>
<td>0.62 ± 0.28*</td>
<td>43.84 ± 13.99</td>
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<tr>
<td></td>
<td>YN</td>
<td>16.81 ± 9.21</td>
<td>5.45 ± 5.90</td>
<td>3.32 ± 3.15</td>
<td>1.55 ± 1.31</td>
<td>7.22 ± 4.43</td>
<td>0.61 ± 0.21</td>
<td>0.53 ± 0.14</td>
<td>47.95 ± 27.89</td>
</tr>
<tr>
<td>60-s Stand</td>
<td>KHT</td>
<td>10.32 ± 6.47*</td>
<td>4.55 ± 2.72*</td>
<td>2.62 ± 2.20</td>
<td>1.71 ± 1.64</td>
<td>7.67 ± 7.56</td>
<td>1.48 ± 0.49*</td>
<td>1.33 ± 0.48*</td>
<td>7.43 ± 5.74</td>
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<tr>
<td></td>
<td>YN</td>
<td>14.19 ± 15.49</td>
<td>3.09 ± 2.50</td>
<td>2.43 ± 1.48</td>
<td>1.24 ± 0.84</td>
<td>6.03 ± 5.04</td>
<td>1.10 ± 0.48</td>
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<td>9.29 ± 5.96</td>
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<td>Steady stand (90 s)</td>
<td>KHT</td>
<td>6.91 ± 5.07*</td>
<td>2.83 ± 1.14</td>
<td>1.79 ± 1.74</td>
<td>1.45 ± 1.85</td>
<td>5.79 ± 3.82</td>
<td>1.64 ± 0.49</td>
<td>1.32 ± 0.45</td>
<td>5.35 ± 6.93</td>
</tr>
<tr>
<td></td>
<td>YN</td>
<td>10.91 ± 13.09</td>
<td>2.11 ± 1.36</td>
<td>2.52 ± 3.33</td>
<td>0.93 ± 0.92</td>
<td>6.82 ± 7.69</td>
<td>1.25 ± 0.32</td>
<td>1.20 ± 0.27</td>
<td>6.04 ± 5.77</td>
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<td>5-min Stand</td>
<td>KHT</td>
<td>5.06 ± 8.21*</td>
<td>2.28 ± 3.21</td>
<td>0.81 ± 0.83</td>
<td>0.78 ± 1.05</td>
<td>6.39 ± 4.15</td>
<td>1.42 ± 0.73</td>
<td>1.05 ± 0.33</td>
<td>4.74 ± 4.65</td>
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<tr>
<td></td>
<td>YN</td>
<td>11.34 ± 19.14</td>
<td>2.92 ± 5.52</td>
<td>1.97 ± 2.56</td>
<td>0.91 ± 1.23</td>
<td>5.39 ± 3.33</td>
<td>1.09 ± 0.34</td>
<td>1.05 ± 0.33</td>
<td>5.99 ± 4.92</td>
</tr>
<tr>
<td>50% HG</td>
<td>KHT</td>
<td>1.19 ± 0.57*</td>
<td>1.13 ± 1.45</td>
<td>0.60 ± 0.36</td>
<td>0.85 ± 1.02</td>
<td>2.39 ± 1.00</td>
<td>0.99 ± 0.37</td>
<td>0.76 ± 0.18</td>
<td>2.23 ± 0.92</td>
</tr>
<tr>
<td></td>
<td>YN</td>
<td>2.28 ± 1.39</td>
<td>0.98 ± 0.76</td>
<td>1.08 ± 1.22</td>
<td>0.58 ± 0.69</td>
<td>4.36 ± 4.31</td>
<td>1.66 ± 2.22</td>
<td>0.76 ± 0.30</td>
<td>4.06 ± 2.18</td>
</tr>
<tr>
<td>100% HG</td>
<td>KHT</td>
<td>4.29 ± 3.84</td>
<td>4.16 ± 6.37</td>
<td>1.02 ± 0.67</td>
<td>1.36 ± 1.59</td>
<td>5.19 ± 4.54</td>
<td>0.97 ± 0.51</td>
<td>0.72 ± 0.18</td>
<td>7.50 ± 5.81</td>
</tr>
<tr>
<td></td>
<td>YN</td>
<td>4.73 ± 4.99</td>
<td>2.02 ± 2.42</td>
<td>1.17 ± 1.51</td>
<td>0.69 ± 0.81</td>
<td>8.11 ± 10.84</td>
<td>1.28 ± 1.75</td>
<td>0.65 ± 0.34</td>
<td>11.25 ± 6.17</td>
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<tr>
<td>HG recovery</td>
<td>KHT</td>
<td>9.12 ± 1.18</td>
<td>1.09 ± 0.59</td>
<td>1.64 ± 2.32</td>
<td>0.92 ± 0.25*</td>
<td>2.02 ± 1.20</td>
<td>0.95 ± 0.31</td>
<td>0.79 ± 0.37</td>
<td>3.35 ± 1.72</td>
</tr>
<tr>
<td></td>
<td>YN</td>
<td>3.95 ± 3.27</td>
<td>1.17 ± 0.48</td>
<td>3.05 ± 3.57</td>
<td>1.19 ± 0.51</td>
<td>1.80 ± 1.41</td>
<td>1.6 ± 1.56</td>
<td>0.93 ± 0.27</td>
<td>4.11 ± 2.11</td>
</tr>
</tbody>
</table>

Values are means ± SE. CP, change in posture; HG, handgrip; BP, blood pressure; LF, low frequency; LF norm, normalized LF; HF, high frequency; HF norm, normalized HF; LF/HF, LF-to-HF ratio; \(\alpha\), \(\alpha_{norm}\), \(\alpha_{norm}\), normalized \(\alpha\); LF BP, LF content of peripheral blood pressure; \(\alpha_{norm}\), \(\alpha_{norm}\), \(\alpha_{norm}\), normalized \(\alpha\); LF BP, LF content of peripheral blood pressure; \(\alpha_{norm}\), \(\alpha_{norm}\), \(\alpha_{norm}\), normalized \(\alpha\). *P < 0.05, significant difference from YN over this time period; †P < 0.05, ANOVA of this point vs. rest different between groups.
absolute power of a given component by the power in that frequency at rest. From these parameters, the time-dependent LF/HF-to-HFHR ratio and α-index were calculated (7, 8, 17). The α-index is based on the understanding that each spontaneous oscillation in BP elicits an oscillation of similar frequency in the R-R interval by effect of the arterial baroreflex activity (25) and is used as a noninvasive index of baroreflex sensitivity. The time-dependent α-index was calculated by taking the square root of the LFHR(t) over the LFBP(t). Integrals over the relevant frequency ranges were examined as a function of time, every second, and then averaged for statistical analysis.

Statistical analysis. Data are presented as means ± SE. Statistical comparisons were made with the use of statistical analysis software (version 11, SPSS; Chicago, IL). Because of skewed distribution, all frequency parameters [LFHR(t), HFHR(t), HFResp(t), and LFHR(t)] and their derivatives were natural log transformed. Resting values were compared by independent sample t-test. Integrals averaged over the entire rest epoch, and each 15-s period during the stand test was compared by repeated-measures ANOVA. A P value of <0.05 was considered significant, and only significant differences are reported. Because time to exhaustion varied among subjects during HG, average values were calculated as a function of time to exhaustion rather than on an absolute time basis (29). Integrals were averaged over each quartile of effort from rest to fatigue and at minute 1 and minutes 2–5 of recovery and compared between groups by repeated-measures ANOVA.

RESULTS

Examination of our results indicates that autonomic challenges were necessary to distinguish between groups. During supine rest, there were no differences between the groups in any parameters. Results are presented according to challenge for clarity. Table 1 shows the detailed values of all measured parameters.

Change of posture. In both groups, HR increased significantly at CP (from 63 ± 6.2 to 94.6 ± 12.3 in KHT, and from 64 ± 13.4 to 95.0 ± 12.9 in YN). Thirty seconds after CP, YN displayed a more gradual decrease in HR than did KHT (decrease to 76.9 ± 11.1 s at 30 s in KHT and to 84.1 ± 16.5 s in YN). At 45 s, HR was almost exactly the same in both groups (75 beats/min in KHT, 76 in YN). From minute 1 to minute 2, HR of KHT stabilized ~79 beats/min, whereas that of YN fluctuated between 73 and 75 beats/min, and HR of KHT remained higher throughout the rest of stand. The HR over the first 1.5 min after CP was different between groups (P ≤ 0.001). Mean arterial pressure decreased from 77.7 ± 9.4 to 60.0 ± 17.8 mmHg in KHT and from 79 ± 8.7 to 68.4 ± 22.4 mmHg in YN during the first 15 s of stand then stabilized at 79.8 ± 14.2 and 82.6 ± 20.2 mmHg in KHT and YN, respectively. There were no significant differences between the groups in BP response.

CP: frequency parameters for HR. An example of the analysis of the HR is displayed in Fig. 1. Figure 2 shows the group-averaged LFHR values during rest and CP. The LFHR fluctuations in the KHT demonstrated an increased responsiveness to CP compared with the YN (P < 0.05). When normalized to baseline, the LFHRnu for the first minute was also significantly different between the groups (P ≤ 0.05) with the KHT obtaining higher peak values and having higher values than YN for the first 45 s.

In each group, HFHR fluctuations decreased significantly from rest to the end of the stand period. There was no difference between groups in the HFHR.

CP: frequency parameters for BP. An example of the analysis of the BP is displayed in Fig. 3. LFBP in-

![Fig. 1. Heart rate (HR) response to active change of posture (CP) in a normal subject [HR measured in beats/min (BPM)]. Transition to stand occurred at 4,424 s. A: HR; B: time-dependent spectrum of HR; C: time-dependent power in the low-frequency (LF) region (LFHR); D: time-dependent power in the high-frequency (HF) HR region (HFHR); E: LFHR-to-HFHR ratio. Note the marked increase in LF power and the decrease in HF power on CP, indicating a shift in the sympathovagal balance toward sympathetic predominance.](http://ajpheart.physiology.org/10.1152/ajpheart.00170.2003)
increased during the transition to stand similarly in both groups and remained elevated above resting values for the first 2 min of stand. There were no differences in the LFBP during CP between the groups.

CP: a-index. During the transition from rest to stand, KHT had significantly less of a decrease in the a-index (P ≤ 0.05) in both absolute and normalized units than did YN (Fig. 4). Over the entire first minute of the stand, a-index was significantly different between the groups (P ≤ 0.05).

Isometric HG. There were no differences between the KHT and YN in maximal HG strength (20.75 ± 7.14 vs. 18.8 ± 8.2 kg), time to exhaustion (193.3 ± 94 vs. 171.1 ± 69.1 s), or changes in breathing frequency (average of 2 breaths/min increase in both groups during HG). Because respiration changed similarly in both subject groups, we assume that any changes in R-R interval variability induced by changes in breathing depth and/or frequency affected both groups similarly.

Both HR and BP increased significantly with HG. Change in HR during HG was different between groups (P ≤ 0.05) with KHT having lesser increases in HR than YN (60.9 ± 6.9 beats/min in KHT and 64.6 ± 11.5 beats/min in YN increased to 84.6 ± 10.6 and 93.0 ± 16.5 beats/min, respectively). HR returned to resting levels in both groups by the end of the 5-min recovery. Resting MAP was 78.7 ± 10.5 mmHg in KHT versus 81.4 ± 20.7 mmHg in YN and rose to 150.98 ± 24.98 and 159.86 ± 26.21 mmHg, respectively. There were no differences between the groups in mean BP, maximal BP, or percent change in BP with HG.

Isometric HG: frequency parameters for HR. HFHR decreased significantly (P ≤ 0.05) from rest to maximal effort in both groups (Fig. 5). HFHR from 100% effort to the end of a 5-min recovery was significantly different between the groups over time (P ≤ 0.05) with YN having a much sharper increase in HFHR on recovery. There was a similar, significant increase in LFHR over time in both groups from rest to 100% effort. In both groups, absolute values of LF initially (first 50% of effort) declined from resting values and only began to increase at 50% of maximal effort. By the end of recovery, LF values returned to baseline levels in both groups.

LFHR/HFHR, which reflects the sympathovagal balance, changed significantly from rest to maximal effort and through recovery. The response was qualitatively similar between groups. Sympathovagal balance increased from rest to 25% effort and then remained steady through 75% of the HG. From 75% to maximal effort, there was another increase in the LFHR-to-HFHR ratio. These changes must be viewed in perspective of the changes in each frequency range individually. Accordingly, the increases in the LFHR/HFHR at the initiation of HG (due to a greater reduction in HFHR than in LFHR) and from 75% to 100% (caused by further increase in LFHR) effort likely both indicate a shift toward sympathetic predominance.

Isometric HG: frequency parameters for BP. LFBP increased significantly from rest to maximal effort (P ≤ 0.05) in both groups and then declined on recovery (Fig. 6). In a pattern similar to that of the LFHR, LFBP was fairly stable through the first 50% of the effort, and...
the majority of the increase in LF\textsubscript{BP} occurred from 50% to 100% maximal effort.

**DISCUSSION**

Both groups in this study consisted of age, sex, and BMI-matched, young, normotensive subjects. They differed only in the genetic propensity for developing hypertension later in life. No differences in autonomic control between the groups were discernable at rest. Implementation of autonomic challenges creating abrupt transients in cardiovascular signals allowed us to observe subtle, yet significant, malfunctions in both branches of the autonomic nervous system in KHT. To the best of our knowledge, this is the first study utilizing noninvasive techniques that demonstrates autonomic malfunction in young, still-normotensive offspring of hypertensive parents.

During CP, we observed a significantly greater increase in LF\textsubscript{HR} in KHT versus YN, whereas HF\textsubscript{HR} decreased similarly in both groups. An increase in LF\textsubscript{HR} in conjunction with a decrease in HF\textsubscript{HR} indicates a reduction in vagal activity and an increase in sympathetic activity (30). This response indicates significantly greater sympathetic activation in KHT versus YN, concurrent with attenuated baroreceptor responsiveness in KHT, as expressed by the \( \alpha \)-index. In addition, KHT displayed reduced vagal reactivation on recovery from isometric HG. The ability to noninvasively discern elevated sympathetic activation and lower vagal reactivation in normotensive individuals with a predisposition to the development of hypertension is remarkable.

**Evidence of increased sympathetic activity.** Although members of the two groups exhibited similar increases in HR on stand, KHT required greater \( \beta \)-sympathetic activation (expressed by a larger increase in LF\textsubscript{HR}) to achieve the same increase in HR. HR in KHT dropped more quickly after the transition, despite sustained higher LF activity. In addition, although increases in LF\textsubscript{HR} during HG were similar, KHT had significantly lower HR during the entire course of the HG procedure, reinforcing the idea that greater sympathetic activity is necessary to elevate HR in the KHT. Although they are still fully normotensive, KHT display \( \beta \)-sympathetic overactivity, or a reduced responsiveness to \( \beta \)-sympathetic activity (necessitating a greater sympathetic activity), in response to both CP and isometric HG.

Our results of slightly reduced LF\textsubscript{HR} at rest in KHT, followed by a larger increase in LF\textsubscript{HR} on standing, are supported by Noll et al.'s (22) findings that both MSNA and plasma NE were insignificantly lower in KHT versus YN at baseline yet increased only in the KHT in response to mental stress. Hyperreactivity of the SNS has long been suspected in the development of HT, but studies have yielded inconsistent results. It is likely that activation of the SNS (20) and impairment in autonomic regulation (16) develop gradually during the progressive stages of early hypertension. In the current study, normotensive individuals with a genetic predisposition for hypertension showed increased sympathetic activity only in response to autonomic perturbations. The detection of this excessive sympathetic activation in response to perturbations and not under resting conditions is supported by Noll et al.'s (22) observation of increased MSNA during mental stress in KHT. Our findings provide further foundation to the contention of Grassi (13) that the adrenergic activation in hypertension is not a consequence of the high BP state but rather plays a pathogenic role, in that its occurrence triggers the elevation in BP and favors the maintenance of the hypertensive state.

**Reduced baroreceptor sensitivity in KHT.** During the transition from rest to stand, the \( \alpha \)-index, a marker of baroreflex sensitivity, changed significantly (\( P \leq 0.05 \)) less in the KHT than in YN. This appears to indicate that the still-normotensive KHT have less baroreflex sensitivity than YN. Pagani and Lucini (23) demonstrated a reduced \( \alpha \)-index in hypertensive individuals.
Lucini et al. (16) have recently shown that the standing-induced reduction in the α-index was progressively smaller with rising pressure levels (from normotensive to hypertensives); however, in their study, differences in the α-index were already apparent at rest. Our results show that, although no differences are discernable at rest, this reduced baroreflex sensitivity is already expressed in its response to stand in normotensive individuals at genetic risk for hypertension.

α-Sympathetic activity unaffected in KHT. On the basis of our results, it appears that in normotensive individuals prone to hypertension, the LF oscillations in BP representative of α-sympathetic activity are not yet affected, as evidenced by similar resting levels and comparable increases in KHT and YN in LFBP during stand and HG. We previously reported (2) enhanced α-sympathetic activity at rest and a markedly reduced responsiveness in mild hypertensives in response to CP. These findings from the previous study in mild hypertensives coincide with Lucini et al.’s (16) recent finding that significant elevations in the LF of systolic arterial pressure were only present in hypertensive individuals and not in individuals with normal or borderline high BP. Because no alterations in LFBP were evident in the current study either at rest or in response to CP, it appears that α-sympathetic activity is not yet affected in these still-normotensive offspring of hypertensive parents.

Reduced vagal reactivation in KHT. On recovery from the isometric HG exercise, KHT demonstrated a slower recovery of vagal activity. Perhaps this is the beginning of reduced vagal cardiac drive observed in hypertensive subjects (14).

There were no differences between our two groups during the effort phase of isometric HG. The behavior of LF fluctuations in BP corresponds with a report (28) showing that during the first 50% maximal effort of the HG challenge, LF fluctuations did not change significantly, but from 50–100% of maximal effort, LF was increased significantly. Rowell and O’Leary (28) reported that MSNA during isometric exercise rises only after 1–2 min because of the time required for accumulation of metabolites in the muscle. In addition, HR and cardiac output increased during isometric exercise due to vagal withdrawal (28), and we observed decreases in HF of HR during the first 50–75% of maximal effort.

Identification of individuals prone to hypertension may be possible with the use of these noninvasive techniques, by establishing a set of threshold values for autonomic responses to challenges, such as change in posture and isometric HG. Evidence of elevated sympathetic activation at such an early stage of disease progression emphasizes the necessity of targeting reduction in sympathetic activation as a primary goal in the prevention and treatment of HT. Early identification of individuals with a prehypertensive profile will provide an incentive for implementing and adhering to lifestyle modifications, such as weight reduction and implementation of a moderate intensity aerobic exercise program (3, 5), which may delay or prevent the onset of full-blown hypertension.

DISCUSSIONS

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