Early Detection of Essential Hypertension by Time-Frequency Analysis

LR Davrath, Y Goren, I Pinhas, D David, S Akselrod

Tel Aviv University, Tel Aviv, Israel

Abstract

Hypertension affects approximately 25% of adults in industrialized countries and contributes significantly to morbidity and mortality from cardiovascular diseases. Young adult, normotensive offspring of one hypertensive parent (KHT, n=12) and normotensive offspring of two normotensive parents (YN, n=14) participated. ECG, continuous blood pressure, and respiration were recorded. Time-frequency decomposition of these signals was performed by a Continuous Wavelet Transform. During change in posture (CP), KHT demonstrated a significantly greater increase in the low frequency fluctuations in heart rate (HR) than YN, indicating enhanced sympathetic involvement in the HR response to CP. Upon recovery from Handgrip, vagal reactivation was more sluggish in KHT. These results indicate possible malfunctions in both branches of autonomic control in individuals at increased risk of hypertension.

1. Introduction

Approximately one-fourth of the US adult population (approx 50 million people today) has hypertension, increasing to more than 50% among the elderly. Elevations in blood pressure (BP) are associated with increased risk of cardiovascular morbidity and mortality. The public health impact and economic burden of hypertension are immense, making the **early identification of persons at increased risk** for developing hypertension a priority [1].

Given the strength of the genetic component of essential hypertension (up to 60% heritibility), we chose to study adult normotensive offspring of one essential hypertensive parent. Two sympathetic maneuvers were utilized in an attempt to unveil malfunctions in autonomic control indicative of impending hypertension.

Autonomic control can be evaluated by means of real time, non-invasive analysis of the spontaneous fluctuations in cardiovascular signals, such as heart rate and blood pressure. We focused on the instantaneous fluctuations in two main regions of power: a high frequency (HF) peak (in heart rate only), located around the respiratory frequency, typically between 0.18-0.5 Hz, reflecting primarily vagal activity, and a low frequency peak (LF) centered around 0.1 Hz. The LF content of HR fluctuations is an estimate of combined vagal and β-sympathetic activity, while the LF content of BP fluctuations is an estimate of α-sympathetic activity [2,3].

Previous investigations using spectral analysis of HR and BP fluctuations, have led to the detection of autonomic alterations in hypertensive and mild-hypertensive patients [4,5]. Sympathetic enhancement in mild-hypertension was reflected by increased LF of BP fluctuations compared to normotensives whereas vagal withdrawal was correlated with reduced HF fluctuations of RR intervals in the hypertensives [6]. Since the development of hypertension appears to consist of a continuum of damage, we expect to find similar, yet milder autonomic dysfunction in offspring of essential hypertensive parents.

When considering non-steady state conditions such as those resulting from autonomic perturbations, Time-Frequency analysis must be used. The results are a time-dependent spectral decomposition and time-dependent integrals over the relevant frequency bands.

2. Subjects

Two groups of normotensive young subjects were studied. Individuals with one hypertensive parent were categorized as "KHT" while subjects with two normotensive parents were designated "YN". **KHT** (n=12, age 29.6 $\pm$4.3 yr, BMI 24.1 kg/m^2, % fat 22$\pm$5), **YN** (n=14, age 28.7 $\pm$ 3.6 yr, BMI 23.1 kg/m^2, % fat 19.8$\pm$11). This study was approved by the Institutional Review Board of Tel Aviv University, and all subjects signed a written informed consent form. Before participation they were screened with standard health history and physical activity questionnaires. All subjects were non-smokers and individuals with known autonomic disorders were excluded.

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2.1. Protocol

- 30 min quiet, supine rest in a temperature controlled room (22-24 °C)
- 30% maximal voluntary contraction (MVC) Isometric Handgrip until fatigue
- 10 min supine rest
- Active Change in Posture (CP) from supine to standing (5 seconds)
- 5-minute stand test.

2.2. Signal acquisition

The following signals were sampled simultaneously, on-line at a sampling rate of 500 Hz, using a Biopac multi-channel device with the Acknowledge software (MP100-BIOPAC system) and saved to a PC for off-line analysis:

- ECG (leads I, II) from the MP 100 Biopac System ECG 100B amplifier
- Continuous, non-invasive blood pressure using the Portapres device
- Respiration recorded over rib and abdomen by Respitrace pneumoplethysmograph
- Biopac Handgrip force dynamometer and Biopac DA100B Amplifier

3. Signal pre-processing

Calibration interruptions in the continuous BP signal were corrected with an algorithm written in our lab [7]. The corrected BP and respiration signals were low pass filtered (cut off frequency 4 Hz) and decimated to 10 Hz.

R waves from the recorded ECG were detected automatically, and detection was verified manually. Resulting RR intervals were interpolated to an equally spaced HR time series [8] sampled at an effective sampling rate of 10 Hz.

Both HR and BP were filtered through a median high pass filter to avoid the masking effect of non-stationarities on the spectrum. Less than 1% of the beats were corrected in all signals.

4. Time-frequency analysis

Both Time and Frequency Domain were considered for the HR and BP signals. In the frequency domain we use the time-dependent spectral analysis, which reveals the changing amplitude of each frequency component present in the signal.

Time-Frequency decomposition of the signals was performed by a Continuous Wavelet Transform (CWT) [9]. This wavelet transform contains many aspects of the SDA developed in our laboratory [10]. For each time and frequency, the corresponding spectral component is calculated on a windowed segment of the signal. The duration of this segment is inversely proportional to the analyzed frequency. Varying the window duration based on the frequency analyzed allows us to achieve a much better time localization of events in the HF range of the signal, and to quantify much lower frequency components than techniques such as Short Time Fourier Transform allow, thus optimizing both time and frequency resolution.

4.1. Frequency ranges

The time-dependent frequency decomposition of each recorded signal was estimated as described above. Two spectral regions were selected, associated with the LF and HF domains. We then used an algorithm that traces the main frequency in each band and the changes during the entire experiment, and accordingly, accurately determines the time-varying boundaries. Once boundaries of LF and HF peaks were determined, we integrated the CWT over the frequencies of each band in order to obtain time-dependent LF peak [LF(t)] and time dependent HF peak [HF(t)]. The LF(t) and HF(t) integrals of HR, the HF(t) of Respiration, and the LF(t) of BP were calculated. Integrals over the relevant frequency ranges were examined each second, then averaged for statistical analysis.

5. Statistical analysis

Due to skewed distribution, LF(t) and HF(t) were natural log transformed. Resting values were compared by independent sample t-test. Integrals over the entire rest epoch, and each 15- second period during the stand test were compared by repeated measures ANOVA. During handgrip, time to failure was divided into quarters. 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. For both challenges, LF(t) was normalized by LF(*rest*) to reduce individual differences.

6. Results - stand

During supine rest, there were no differences between the groups in any parameters.

HR over the first minute and a half was different between groups ($p \leq 0.001$). YN and KHT had similar increases upon standing, yet YN displayed a more gradual decrease after the stand than KHT. In both groups, HR increased significantly upon standing from resting values of 63 ± 7.2 beats for KHT and 64 ± 11.4 in YN to 94.6 ± 12.3 and 95.5 ± 12.9 respectively, then declined to 75.7 ± 11.1 in KHT and 81.4 ± 17 in YN.

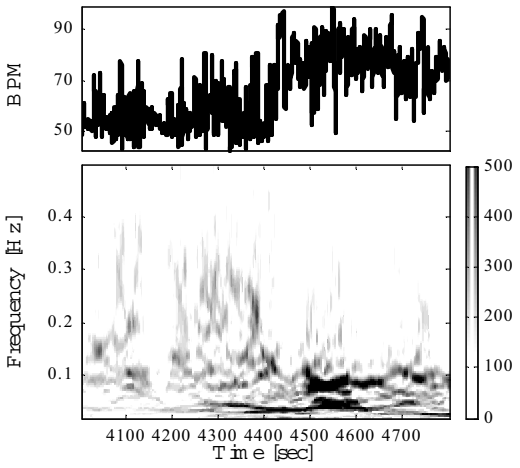

Figure 1. Time-dependent spectrum of HR during rest and standing in a YN subject. Transition to stand occurred at 4424 seconds. Note the increase in LF power upon standing.

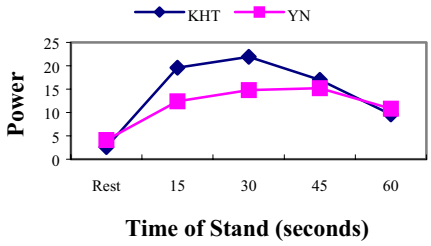

Figure 2. LF of HR from rest through the first minute of stand. Power in BPM^2

LF of HR of the KHT was slightly lower during the rest epoch and rose higher upon standing than in the YN ($p \leq 0.05$).

Normalized LF for the first minute and for the entire 5 min period was also significantly different between the groups ($p \leq 0.05$) with the KHT having higher values than YN for the first minute and 45 seconds, and obtaining higher peak values.

HF of HR decreased significantly from rest to the end of the stand period. There was no difference between groups in the HF of HR.

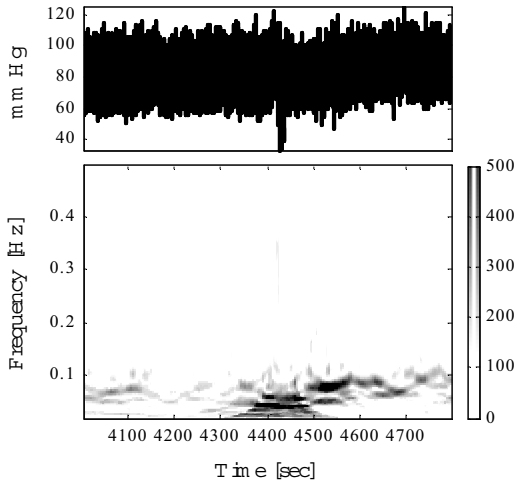

Figure 3. Time-dependent spectrum of BP during rest and standing in the same YN subject. Transition to stand occurred at 4424 seconds.

LF of BP increased during the transition to stand and standing in both groups, and remained elevated above resting values for the first 2 minutes of stand. Blood pressure was not different between the groups during stand.

6.1. Isometric handgrip

Both HR and BP increased with Handgrip. HR during handgrip and recovery was different between groups ($p \leq 0.05$) with KHT having lesser increases in HR than YN.

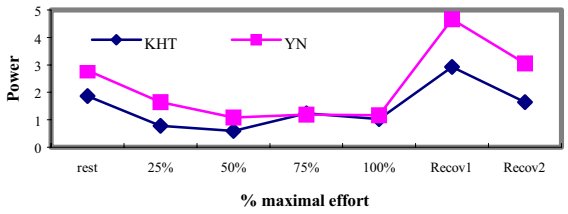

Figure 4. HF of HR during Isometric Handgrip (rest to fatigue from 30%MVC) and recovery. . Power in BPM^2

HF of HR decreased significantly ($p \leq 0.05$) from rest to max effort in both groups. HF from 100% effort to the end of 5 min recovery was significantly different between the groups over time ($p \leq 0.05$) with YN having a sharper increase in HF upon recovery. There was a similar increase in LF of HR over time in both groups although it did not reach significance from rest to 100% effort. LF of BP increased significantly from rest to maximal effort ($p \leq 0.05$), then declined upon recovery.

7. Discussion

Groups in this study were comprised of age-and BMI-matched, young, normotensive subjects. They differed only in the genetic propensity for developing hypertension later in life. We distinguished a difference in response to autonomic challenges in KHT in relation to YN.

β-sympathetic over-activity, or a reduced responsiveness to β-sympathetic activity (necessitating greater activity), already expresses itself in response to active Change in Posture in KHT. Although both groups exhibited similar increases in HR, KHT required greater β-sympathetic activation (expressed by larger increases in LF of HR) to achieve this increase in HR. HR in KHT fell more quickly after the transition, despite higher LF activity. Additionally, although increases in LF of HR during Handgrip were similar, KHT had significantly lower HR, reinforcing the idea that greater sympathetic activity is necessary to elevate HR in the KHT.

Upon recovery from the Isometric Handgrip, KHT demonstrated a slower recovery of vagal activity. Perhaps this is the beginning of reduced vagal cardiac drive observed in hypertensive subjects. There were no differences between groups during the effort phase of Isometric Handgrip.

Apparently, in normotensive individuals prone to hypertension, α-sympathetic activity is not yet affected as evidenced by similar increases in KHT and YN in LF of BP during stand and HG. Although enhancement of vasomotor sympathetic modulation has been reported in hypertensive and mild-hypertensive individuals [6], they are in a more advanced stage of the disease progression than the subjects in our study.

Implementation of autonomic challenges in this study 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 non-invasive techniques that demonstrates a difference in autonomic function in normotensive offspring of hypertensive parents.

Identification of individuals prone to hypertension may be possible using these non-invasive techniques. Early identification of individuals with a pre-hypertensive profile will provide incentive for implementing lifestyle modifications, which may delay or prevent the onset of full-blown hypertension.

Acknowledgements

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Address for correspondence:

Linda Davrath, PhD
The Abramson Center for Medical Physics
Tel Aviv University, P.O. Box 39040,
Tel Aviv 69978, Israel.
lindad@post.tau.ac.il