Epidemiological Study on the Effect of Pre-Hypertension and Family History of Hypertension on Cardiac Autonomic Function

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Objectives
This study sought to examine the hypothesis that cardiac autonomic function (CAF) is altered in pre-hypertensive subjects and normotensive subjects with a family history of hypertension (FHH).

Background
The findings on the FHH effect in CAF have been inconsistent, and little is known about altered CAF in pre-hypertensive subjects under The Seventh Report of the Joint National Commission on High Blood Pressure criteria of normotension and pre-hypertension.

Methods
A total of 1,436 community dwellers were classified as having normotension without FHH (NT[−]), normotension with FHH (NT[+]), pre-hypertension, and hypertension. Cardiac autonomic function was determined by standard deviation of RR intervals (SDNN), power spectrum in low frequencies (LF) and high frequencies (HF) and LF/HF ratio in supine position for 5 min, the ratio between the longest RR interval at approximately the 30th beat and the shortest RR interval at approximately the 15th beat after standing (30 max/15 min ratio), and the ratio between the longest RR interval during expiration and the shortest RR interval during inspiration (E/I ratio).

Results
There was a significant difference in all CAF indexes among subjects with NT[−], NT[+], pre-hypertension, and hypertension. Multivariate analyses with an analysis of covariance model showed that 30 max/15 min ratio, E/I ratio, and HF power decreased in subjects with NT[+], pre-hypertension, and hypertension when compared with NT[−] subjects. Pre-hypertensive and hypertensive subjects displayed higher square roots of LF/HF ratios. Only pre-hypertensive subjects had higher LF power.

Conclusions
Our study provides evidence that CAF plays a role in pre-hypertension and that altered autonomic function is already present in subjects with FHH. An autonomic imbalance shifting with augmented sympathetic tone was more enhanced in pre-hypertension. (J Am Coll Cardiol 2008;51:1896–901) © 2008 by the American College of Cardiology Foundation

Evidence from studies of both animals and humans suggests that the autonomic nervous system plays a crucial role in the development of hypertension and that autonomic dysfunction underlies the initiation and maintenance of hypertension (1–6). Several studies have revealed that hypertensive subjects manifested an impaired cardiac autonomic function (CAF) (7–15). The ratio between the RR intervals during expiration and inspiration (E/I ratio) while deep breathing and the ratio between approximately the 30th and 15th RR intervals after standing from the supine position are the traditional CAF tests of parasympathetic activity (16,17). The CAF tests can also be measured by beat-to-beat changes in the heart rate. The standard deviation of normal-to-normal intervals or RR intervals (SDNN) reflects cardiac vagal activity in the time domain (16). A power spectral density analysis provides the frequency component of heart rate variability (HRV). The low-frequency component (LF) (0.04 to 0.15 Hz) is predominantly under sympathetic control with vagal modulation. Parasympathetic activity is the major contributor to its high-frequency (HF) (0.15 to 0.40 Hz) component. The LF/HF ratio displays the index of sympathovagal balance (16,17).
Recently, the normal cutoff values for blood pressure have been revised to <120/80 mm Hg, and pre-hypertension is defined as a blood pressure of 120 to 139/80 to 89 mm Hg (18). The higher the blood pressure, the greater the chance of heart attacks, heart failure, stroke, and kidney disease in subjects with a blood pressure ranging from 115/75 to 185/115 mm Hg (19). There has been a hospital-based study of CAF in subjects with high-normal blood pressure of 130 to 139/85 to 89 mm Hg (20), rather than the revised value of 120 to 139/80 to 89 mm Hg. The findings of CAF alteration in normotenive subjects with a family history of hypertension (FHH) have been inconsistent (21–23), and these studies define normotension as a blood pressure <140/90 mm Hg (21–23), not the revised value of <120/80 mm Hg. Furthermore, all of the aforementioned studies (20–23) were not population-based. Therefore, we explored the effects of pre-hypertension and FHH on CAF from the epidemiological data collected in Taiwan.

Methods

Participant sample. Community dwellers were recruited from an epidemiological study on chronic diseases conducted in Tainan City, Taiwan, and the details have been described elsewhere (24). A 3-stage sampling method was used to generate a stratified systematic cluster sample of households throughout the city. Initially, the city was divided into 7 strata according to the administrative districts. In each district, 1 area was selected from each stratum by adopting probability proportional to the size of the areas within that specific stratum. Then, every fifth household of each of the 7 selected areas was systematically identified. Finally, all the members of each household ≥20 years of age were invited to take part in the study. A total of 2,416 subjects were eligible from the 7 selected areas, and 1,638 subjects (67.8%) completed the study protocol. Finally, 1,436 participants were included in the analysis after exclusion of 202 subjects who had taken medications known to influence CAF, such as antihypertensive drugs, antiparkinsonism drugs, narcotics, sedatives, and antipsychotic and antidepressant drugs, within 2 weeks of the examination. The study was approved by the research committee of the National Cheng Kung University Hospital in Taiwan, and written consent was obtained from all participants.

Clinical examination. All subjects were instructed not to consume alcohol, coffee, tea, or cigarettes on the day of the examination. Demographic characteristics, medical history, medication use, FHH, dietary habits, cigarette smoking, alcohol drinking, and physical activity were assessed by a well-trained assistant with a structured questionnaire. A positive FHH was confirmed when at least 1 of the subject’s parents had a documented history of hypertension (22). Total physical activity, including work, walking, and leisure time exercise, was measured in metabolic equivalent-hours/week over the past year (25). Wearing only light indoor clothes and no shoes, all subjects were measured for body weight and height by well-trained nurses. The laboratory tests included blood biochemistry, a hemogram, a urine examination, and an electrocardiogram (ECG) after an overnight fast of at least 10 h. The subjects without a history of diabetes received a 75-g oral glucose tolerance test after completion of the measurement of their blood pressure and HRV. A blood sample was obtained 2 h after the subjects drank the glucose solution.

Blood pressure was measured with a DINAMAP vital sign monitor (Model 1846SX, Critikon Inc., Irvine, California) in a quiet environment. Measurements were obtained from subjects who had been in a fasting state between 8:00 AM and 10:00 AM, and an appropriate-sized cuff was wrapped around the right upper arm of each study subject. Two readings of the blood pressure and heart rate while seated were separated by at least 5 min after the subject had been at rest for at least 15 min. According to the Seventh Report of the Joint National Commission on High Blood Pressure (JNC 7) criteria, the average of 2 seated readings of blood pressure can be classified as normotension (blood pressure <120/80 mm Hg without history of hypertension), pre-hypertension (blood pressure of 120 to 139/80 to 89 mm Hg without history of hypertension), and hypertension (blood pressure of ≥140/90 mm Hg or a documented history of hypertension) (18).

Measurements of HRV. Before the start of the HRV assessment, the subjects rested in a supine position for at least 15 min. The RR intervals for the beat-to-beat duration of the cardiac cycle were measured continuously with an ECG monitor (CardiSuny α 800, Fukuda M-E Kogyo Inc., Tokyo, Japan) on a personal computer-based data-acquisition system according to the following sequence: 1) normal breathing for 5 min while in a supine position; then 2) an active change from the lying to the standing position; and finally 3) 6 deep breaths over 1 min while sitting after a 10-min rest. The analog signals were immediately sent to the signal-acquiring and processing system (DAQPad-6020E and SCB-68, National Instruments, Austin, Texas) and stored in a personal computer. The ECG signals were processed for R-peak detection with the LabView 6.1 software program (National Instruments). A power spectral analysis was used to define the temporal fluctuations of the HRV. The LF
(0.04 to 0.15 Hz) and HF (0.15 to 0.4 Hz) components were identified by conducting a Fourier transform analysis for each subject (16,17). The E/I ratio was the ratio between the longest RR interval during expiration and the shortest RR interval during inspiration. The ratio between the longest RR interval at approximately the 30th beat and the shortest RR interval at approximately the 15th beat after standing (30 max/15 min ratio) was also evaluated (16,17). The examination protocol, labels, definitions, and meaning of the CAF tests are summarized in Table 1.

### Statistical analyses

Data analyses were performed with the Statistical Package for Social Sciences 10.0 for Windows (SPSS Inc., Chicago, Illinois). The subjects were divided into 4 groups, including normotension without FHH (NT(−)), normotension with FHH (NT(+)), pre-hypertension, and hypertension. In the univariate analysis, analysis of variance was used to compare continuous variables among different blood pressure groups and the Kruskal-Wallis test was used for comparison of the plasma triglyceride and physical activity level. Bonferroni post hoc tests were also used to compare CAF, indicated by SDNN, E/I ratio, 30 max/15 min ratio, LF and HF power, and the square root of the LF/HF ratio, among groups. Comparisons of categorical variables were made with the chi-square or Fisher exact test, where appropriate.

Analysis of covariance (ANCOVA) was used to compare the CAF among different blood pressure groups with adjustment for other confounders. The confounders included age, gender, body mass index, current alcohol use, plasma glucose, cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C), which differed significantly among the different blood pressure groups on the basis of univariate analysis. A p value <0.05 was considered significant.

### Results

The subjects were classified as NT(−) (n = 630), NT(+) (n = 315), pre-hypertension (n = 340), and hypertension (n = 153) according to JNC 7 criterion. Table 2 reveals the comparisons of clinical variables among subjects with NT(−), NT(+), pre-hypertension, and hypertension. There were significant differences in age, gender, body mass index, the average of 2 seated systolic/diastolic blood pressure and heart rate, fasting plasma glucose, cholesterol, triglyceride, HDL-C, and the prevalence of current alcohol use among these 4 groups.

Table 3 shows the univariate analysis for the comparisons of CAF among subjects with NT(−), NT(+), pre-hypertension, and hypertension. All of the indexes of parasympathetic tone, including SDNN, E/I ratio, 30 max/15 min ratio, and HF power, were significantly different among these 4 groups. Both the LF power, representing predominantly sympathetic drive with vagal modulation, and the square root of the LF/HF ratio, an index of sympathovagal balance, also apparently differed among these 4 groups. The following results were analyzed with a post hoc test. Compared with NT(−) subjects, both prehypertensive and hypertensive subjects had significantly lower SDNN, E/I ratios, 30 max/15 min ratios, and HF power, but they had higher square roots of LF/HF ratios. In addition, NT(+) subjects had lower HF power than that of NT(−) subjects. Pre-hypertensive subjects exhibited higher LF power than that of NT(−) subjects. Compared with NT(+) subjects, both prehypertensive and hypertensive subjects had significantly lower SDNN, E/I ratios, and HF power but higher square roots of LF/HF ratios. Hypertensive subjects also displayed a lower 30 max/15 min ratio than that of NT(+) subjects. Finally, hypertensive subjects suffered from lower SDNN and E/I ratios than those of pre-hypertensive subjects.

Figure 1 shows a comparison and adjusted means of CAF among different blood pressure groups with adjustment for other confounders from ANCOVA. When compared with NT(−) subjects, NT(+), pre-hypertensive, and hypertensive subjects had a lower parasympathetic drive, as indicated by the E/I ratio, the 30 max/15 min ratio, and HF power. However, SDNN was not apparently different among NT(−), NT(+), pre-hypertensive, and hypertensive sub-

### Table 1: Examination Protocol, Label, Definition, and Meaning of CAF Tests

<table>
<thead>
<tr>
<th>Examination Protocol</th>
<th>Label</th>
<th>Definition</th>
<th>Meaning of CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal breathing for 5 min while in a supine position after a 15-min rest period</td>
<td>LF/HF ratio</td>
<td>The ratio between LF power and HF power</td>
<td>Sympathovagal balance</td>
</tr>
<tr>
<td></td>
<td>LF power (ms²)</td>
<td>Low-frequency (0.04–0.15 Hz) power in supine position for 5 min</td>
<td>Predominantly sympathetic with parasympathetic modulation</td>
</tr>
<tr>
<td></td>
<td>HF power (ms²)</td>
<td>High-frequency (0.15–0.40 Hz) power in supine position for 5 min</td>
<td>Parasympathetic modulation</td>
</tr>
<tr>
<td></td>
<td>SDNN (ms)</td>
<td>The standard deviation of RR interval in supine position for 5 min</td>
<td>Parasympathetic modulation</td>
</tr>
<tr>
<td>2. An active change from the supine to standing position</td>
<td>30 max/15 min ratio</td>
<td>The ratio between the longest RR interval at approximately the 30th beat and the shortest RR interval at approximately the 15th beat after standing</td>
<td>Parasympathetic modulation</td>
</tr>
<tr>
<td>3. Deep breathing at a rate of 6 breaths/min while sitting after a 10-min rest period</td>
<td>E/I ratio</td>
<td>The average of 6 ratios between the longest RR interval during expiration and the shortest RR interval during inspiration</td>
<td>Parasympathetic modulation</td>
</tr>
</tbody>
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CAF = cardiac autonomic function; HF = high frequency; LF = low frequency.
jackets. Regarding the predominantly sympathetic drive with partial parasympathetic modulation of heart, pre-hypertensive subjects had higher LF power than that of NT(−) subjects, but neither NT(+) subjects nor hypertensive subjects exhibited higher LF power than that of NT(−) subjects after adjustment for other variables. In the sympathovagal balance domain, both pre-hypertensive and hypertensive subjects displayed higher square roots of LF/HF ratios than those of NT(−) subjects, but there was no difference in the square roots of LF/HF ratios between NT(+) and NT(−) subjects after adjustment for other confounders. In summary, parasympathetic drive decreased in subjects with NT(−), pre-hypertension, and hypertension. The square root of the LF/HF ratio decreased in both the pre-hypertension and hypertension individuals, but an increase in LF power existed only in subjects with pre-hypertension.

Discussion

Our study provides the epidemiological evidence that an altered CAF is present in subjects with NT(+) and pre-hypertension after carefully controlling for confounding factors. By mapping the CAF across different blood pressure groups, from NT(−), NT(+), then to pre-hypertension, and finally to hypertension, our study reveals that decreased parasympathetic modulation of the heart, shown by a declined 30 max/15 min ratio and HF power, exists in NT(+) subjects, and this impairment of parasympathetic drive also occurs in subjects with either pre-hypertension or hypertension. In contrast, the LF power, which indicates predominantly sympathetic control with parasympathetic modulation (17), is enhanced in the case of pre-hypertension but not in those of NT(+) and hypertension.

Regarding the CAF in NT(+) subjects, our results reveal that there is a significant decline of the parasympathetic drive, reflected by a decreased 30 max/15 min ratio and HF power, but not LF power. The result is compatible with another study that showed a decreased HF power in normotensive subjects with FHH (21), although some reports also have indicated an increase of LF power in normotensive subjects with FHH (22,23). Because all pre-

Table 2

| Table 2 Comparison of Clinical Variables Among Subjects With Different Blood Pressure, Including Normotension With and Without a Family History of Hypertension, Pre-Hypertension, and Hypertension |
|-------------|-------------|-------------|-------------|-------------|-------------|
| Age, yrs    | NT(−) (n = 630) | NT(+) (n = 315) | Pre-Hypertension (n = 340) | Hypertension (n = 153) | p Value     |
| Male, %     | 41.5         | 39.6         | 59.7         | 60.1         | <0.001      |
| BMI, kg/m²  | 22.8 ± 3.3   | 22.7 ± 2.8   | 106.8 ± 6.8  | 25.0 ± 3.7   | <0.001      |
| SBP, mm Hg  | 105.7 ± 7.0  | 106.8 ± 6.8  | 127.2 ± 6.4  | 162.8 ± 15.0 | <0.001      |
| DBP, mm Hg  | 66.0 ± 6.6   | 66.3 ± 6.5   | 75.8 ± 7.0   | 86.3 ± 10.7  | <0.001      |
| HR, beats/min | 64.8 ± 11.0  | 65.1 ± 10.2  | 67.9 ± 12.8  | 69.2 ± 12.9  | <0.001      |
| Physical activity, MET-h/week* | 60.4 ± 88.0  | 66.5 ± 111.1 | 54.2 ± 58.0  | 55.5 ± 58.8  | 0.227       |
| Fasting glucose, mmol/l | 5.1 ± 1.0    | 5.0 ± 0.6    | 5.7 ± 2.0    | 6.1 ± 2.5    | <0.001      |
| Cholesterol, mmol/l | 4.8 ± 1.0    | 4.8 ± 1.0    | 5.2 ± 1.2    | 5.3 ± 1.1    | <0.001      |
| Triglyceride, mmol/l* | 1.2 ± 0.8    | 1.2 ± 0.7    | 1.7 ± 2.2    | 1.7 ± 1.2    | <0.001      |
| HDL-C, mmol/l | 1.4 ± 0.4    | 1.4 ± 0.4    | 1.3 ± 0.3    | 1.3 ± 0.3    | 0.003       |
| Current alcohol use, % | 10.4         | 10.4         | 18.2         | 17.6         | 0.002       |
| Current smoking, % | 19.9         | 18.0         | 24.7         | 24.2         | 0.112       |

*Kruskal-Wallis test.

Univariate Analysis for the Comparison of Cardiac Autonomic Function Among Subjects With Different Blood Pressure, Including Normotension With and Without a Family History of Hypertension, Pre-Hypertension, and Hypertension

| Table 3 Univariate Analysis for the Comparison of Cardiac Autonomic Function Among Subjects With Different Blood Pressure, Including Normotension With and Without a Family History of Hypertension, Pre-Hypertension, and Hypertension |
|-------------|-------------|-------------|-------------|-------------|-------------|
| 1. Parasympathetic modulation | NT(−) (n = 630) | NT(+) (n = 315) | Pre-Hypertension (n = 340) | Hypertension (n = 153) | p Value     |
| SDNN, ms    | 40.8 ± 28.9 | 38.7 ± 20.9 | 32.6 ± 20.8† | 25.3 ± 14.9†† | <0.001      |
| E/I ratio   | 1.28 ± 0.12 | 1.27 ± 0.12 | 1.22 ± 0.15† | 1.16 ± 0.12†† | <0.001      |
| 30 max/15 min ratio | 1.14 ± 0.13 | 1.11 ± 0.14 | 1.09 ± 0.14* | 1.06 ± 0.09†† | <0.001      |
| HF power, ms² | 388.1 ± 206.8 | 340.6 ± 206.5 | 268.4 ± 186.1†† | 246.1 ± 184.5†† | <0.001      |
| 2. Predominantly sympathetic with parasympathetic modulation, LF power, ms² | 746.4 ± 403.0 | 801.4 ± 444.2 | 860.0 ± 468.0* | 803.9 ± 449.1 | <0.001      |
| 3. Sympathovagal balance | Square root of LF/HF ratio | 1.63 ± 0.97 | 1.87 ± 1.20 | 2.42 ± 1.88†† | 2.25 ± 1.32†† | <0.001      |

Bonferroni post hoc test: 1) compared with NT(−); *p < 0.001, †p < 0.05; 2) compared with NT(+)†; †p < 0.001; 3) compared with pre-hypertension; †p < 0.01, ††p < 0.001.

Abbreviations as in Tables 1 and 2.
vious studies defined normotension as a blood pressure <140/90 mm Hg (21–23) and not <120/80 mm Hg, some of their normotensive subjects might have had a blood pressure $\geq$120/80 mm Hg; therefore, they should be classified as pre-hypertension according to JNC 7 criterion. This might result in a classification bias and explain the discrepancy between our study and other research (22,23).

As for the effect of pre-hypertension on the CAF, our study shows that pre-hypertension was positively related to LF power and the LF/HF ratio but negatively related to the E/I ratio, 30 max/15 min ratio, and HF power. The result suggests that pre-hypertensive subjects manifest a significantly impaired parasympathetic activity and an enhanced sympathetic modulation of the heart. However, 1 hospital-based study has shown that subjects with a high-normal blood pressure of 130 to 139/85 to 89 mm Hg had a higher LF power than normotensive subjects, but the HF power was not apparently different between subjects with normotension and high normal blood pressure (20). The racial factor (26), subject selection, and different definitions of normotension and pre-hypertension (or high-normal blood pressure) might be the explanation for the discrepancy between this hospital-based study and our study.

In our study, pre-hypertensive subjects have a decreased parasympathetic drive with an autonomic imbalance shifting with augmented sympathetic tone when compared with NT(−) subjects. This might be related to a hemodynamic transition from normotension to pre-hypertension, which is similar to the change from normotension to borderline hypertension that has been characterized by an elevated
cardiac output and normal vascular resistance (27). This high cardiac output has been associated with both an increased cardiac sympathetic drive and a decreased parasympathetic tone in pharmacological blockade studies (3,27). Our hypertensive subjects show—regarding the change in the CAF from pre-hypertension to hypertension—a significant decline in E/I ratio, 30 max/15 min ratio, and HF power, but the LF power did not apparently increase. Thus, the impairment of the cardiac parasympathetic drive exists in hypertension, but the autonomic imbalance with an augmented sympathetic shift is not significantly enhanced. This is consistent with other studies that displayed a decreased cardiac vagal control in hypertensive subjects (9,13). The mechanism underlying the absence of a significant elevation of LF powers in the case of hypertension might be related to the downregulation of the sympathetic tone during the transition from a high cardiac output in pre-hypertension to a high resistance in hypertension (3,27).

A recent study has found that African Americans suffer lower SDNN and HF and LF powers than whites, but no significant differences in HRV parameters were found between African Americans and Hispanics (26). Because race is a potential influence of HRV (26) and our findings are in a Chinese population, further studies are needed in other populations. Another limitation is that our study design is cross-sectional, and the effects of pre-hypertension and FHH on CAF estimated from our result need to be confirmed by longitudinal study.

Conclusions

In conclusion, an impaired parasympathetic drive is already present in normotensive subjects with an FHH, and it also exists in subjects with pre-hypertension and hypertension. An autonomic imbalance shifting with augmented sympathetic tone is more enhanced in the case of pre-hypertension but not hypertension and normotension with an FHH.

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