Heterogeneity of Cardiorenal Characteristics in Normotensive Subjects

Pierre Fesler, Guilhem du Cailar, Jean Ribstein, Albert Mimran

Abstract—Blood pressure is a marker of elevated risk for cardiovascular disease, even within the normotensive range. The present study evaluates cardiorenal modifications observed in normotensive (<140/90 mm Hg) subjects. Using World Health Organization–International Society of Hypertension definitions, 265 normotensive subjects were categorized as having optimal (n=73), normal (n=84), and high-normal (n=108) blood pressure. Renal hemodynamics and function and cardiac morphology were evaluated by isotopic clearance techniques and ultrasonography, respectively. Urinary albumin excretion was measured in 24-hour urine collections. Body mass index and 24-hour urinary sodium (estimate of sodium intake), as well as left ventricular mass index, relative wall thickness, and glomerular filtration rate and filtration fraction, progressively increased in the optimal to high-normal groups. In contrast, effective renal plasma flow remained constant. Albuminuria was similar in all groups. Of interest, the proportion of subjects with concentric pattern of cardiac geometry (relative wall thickness ≥0.44) increased from 7% in optimal to 13% and 20% in normal and high-normal groups, respectively (P<0.05). Within this normotensive range of blood pressure, left ventricular mass index and relative wall thickness but not albuminuria were linearly correlated to systolic blood pressure; however, no correlation with diastolic blood pressure was found. In conclusion, changes in cardiac geometry and renal hemodynamics (increase in glomerular filtration rate and filtration fraction, an approximate index of glomerular pressure) that could predispose to cardiovascular morbidity and renal risk are already present in normotensive subjects with blood pressure higher than 120/80 mm Hg. (Hypertension. 2004;43:219-223.)

Key Words: normotension ■ renal circulation ■ glomerular filtration rate ■ albuminuria

Blood pressure (BP) is a marker of elevated risk for cardiovascular (CV) disease, even within the normotensive range. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6) and the World Health Organization–International Society of Hypertension (WHO–ISH) guidelines divided the normotensive range of BP (<140/90 mm Hg) into optimal, normal, and high-normal BP groups according to systolic and diastolic arterial pressure values. In the Framingham Heart Study cohort, it was reported that high-normal BP is associated with a risk factor-adjusted hazard ratio for CV disease of 2.5 in women and 1.6 in men as compared with optimal BP. A recent meta-analysis of 61 prospective observational studies of BP and mortality showed that above 115/75 mm Hg, each increment of 20 mm Hg in systolic BP (SBP) or of 10 mm Hg in diastolic BP (DBP) is associated with a doubling of the risk of CV events.

In the present study, using the optimal BP group as the reference group, we assessed cardiorenal modifications associated with normal or high-normal BP. In addition, characteristics of subjects with prehypertension as defined in the seventh JNC report, which includes subjects with normal or high-normal BP, was performed.

Methods

Study Population

The study population consisted in 265 normotensive subjects (128 women and 137 men, aged 14 to 77 years), including medical students, hospital employees, or subjects recruited from the outpatient clinic of the department of medicine where individuals came for global health evaluation. Normotension was defined as arterial pressure <140/90 mm Hg on at least two subsequent visits. None of the subjects had ever received antihypertensive therapy. Patients with clinical evidence of atherosclerosis (stroke, coronary and peripheral artery disease), heart failure, renal failure (serum creatinine >120 μmol/L), diabetes mellitus (fasting blood glucose >6.7 mmol/L), marked obesity (body mass index ≥35 kg/m²), or a history of alcohol abuse (>5 drinks/d) were excluded. Doppler echocardiography was used to detect valvular lesions in all patients.

BP Measurements

Arterial pressure was measured every 3 minutes with an automatic device (Model 8800; Colin), and reported values are the average of at least 10 measurements after a 10-minute period of rest in the supine position. Subjects were classified according to JNC-6 and WHO–ISH guidelines as optimal (SBP <20 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), or high-normal BP (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg). If the systolic and diastolic BP readings belonged to different categories, the higher of the two readings was used to assign subjects to a BP category. As recently proposed by JNC-7

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guidelines, we also analyzed subjects with prehypertension (SBP 120 to 139 mm Hg or DBP 80 to 89 mm Hg).

Determination of Renal Function

Patients came to the ward with two consecutive 24-hour urine collections for the determination of sodium (as an index of sodium intake), potassium, urea, creatinine, and albumin excretion (urinary albumin excretion measured by radioimmunoassay). Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were estimated by urinary clearances of technetium-99m-DTPA and 131I-ortho iodohippurate, respectively, using the constant infusion technique as previously described. Blood samples were also obtained before clearance determination for the measurement of plasma renin activity and aldosterone concentration (radioimmunoassay, CEA Sorin kit). Measured creatinine clearance using plasma renin activity was lower than that of the optimal group, and stroke volume was derived as end-diastolic minus end-systolic volume. Total arterial compliance was indirectly estimated by the ratio of stroke volume to central pulse pressure.

Statistical Analysis

SPSS for Windows version 11.0 software (SPSS) was used for statistical analysis. Differences in continuous variables between 2 groups were assessed by the Student t test for parametric data, and differences in categorical data were assessed by χ² analysis. Comparison among multiple groups was performed by analysis of variance or covariance with the Bonferroni post hoc test for continuous data and χ² analysis for categorical data. Because of skewed distribution, urinary albumin (µg/min or mg/mmol creatinine), plasma renin activity, and plasma aldosterone were log-transformed before comparison of groups. Simple relationships between renal function parameters, cardiac parameters, and BP were examined by linear regression and calculation of the Spearman correlation coefficient. Two-tailed P<0.05 was considered statistically significant.

Results

Population Characteristics

As summarized in Table 1, the proportions of male gender and urinary sodium were higher in normal and high-normal BP groups when compared with the optimal BP group. Body mass index (BMI) and fasting blood glucose were slightly higher in the high-normal BP group when compared with the optimal BP group. In subjects of the normal and high-normal BP groups, SBP were examined by linear regression and calculation of the Spearman correlation coefficient. Two-tailed P<0.05 was considered statistically significant.

Midwall fractional shortening (an index of LV systolic function) was calculated according to de Simone et al. LV end-diastolic and end-systolic volumes were calculated with the Teichholz formula, and stroke volume was derived as end-diastolic minus end-systolic volume. Total arterial compliance was indirectly estimated by the ratio of stroke volume to central pulse pressure.

Echocardiography

Echocardiographic assessment of left ventricle (LV) morphology was performed by the same observer with an Acuson 128 XP10 (Acuson) with a 2.5- or 3.5-MHz transducer. Technical details were reported elsewhere. LV hypertrophy (LVH) was defined as left ventricular mass index (LVMI) >110 g/m² in females and >127 g/m² in males. Of note, these cutoff values were obtained in a previous local sample of normal subjects with BP <140/90 mm Hg. Concentric and eccentric LVH were defined by the existence of increased (≥0.44) or normal relative wall thickness (RWT), respectively. Concentric remodeling was defined by the finding of normal LV mass associated with increased RWT.

| TABLE 1. Population Characteristics According to Blood Pressure Category |
|-----------------------------|---|---|---|---|
|                             | Optimal | Normal | High Normal | Prehypertension |
| n                           | 73       | 84     | 108          | 192            |
| Male gender (%)             | 30   | 60*    | 59*          | 60*            |
| Age (y)                     | 32±12     | 33±13   | 37±15       | 35±14          |
| Casual systolic blood pressure (mm Hg) | 113±6 | 124±3* | 135±3*†     | 130±6*         |
| Casual diastolic blood pressure (mm Hg) | 67±7 | 72±6* | 78±7*†       | 75±7*          |
| Casual heart rate (bpm)     | 67±12     | 65±10   | 65±9        | 65±10          |
| Smokers (%)                 | 23       | 28      | 25          | 26             |
| Family history of hypertension (%) | 29 | 36      | 62*†        | 51*            |
| Body mass index (kg/m²)     | 22.8±3.5   | 24.0±3.3 | 24.5±3.3*   | 24.2±3.3*      |
| Serum creatinine (µmol/L)   | 81±1      | 83±1    | 80±1        | 82±1           |
| Serum uric acid (µmol/L)    | 262±63    | 282±85  | 279±76      | 280±80         |
| Fasting blood glucose (mmol/L) | 4.4±0.6 | 4.5±0.7 | 4.7±0.7*    | 4.6±0.7*       |
| Total cholesterol (mmol/L)  | 4.98±0.90 | 5.11±1.01 | 5.24±0.95 | 5.16±0.95      |
| HDL cholesterol (mmol/L)    | 1.32±0.41 | 1.34±0.44 | 1.39±0.39   | 1.37±0.41      |
| Triglycerides (mmol/L)      | 0.97±0.47 | 1.08±0.56 | 1.03±0.46   | 1.05±0.50      |
| Urinary sodium (mmol/24 h)  | 122±46    | 145±53*  | 147±56*     | 144±52*        |
| Urinary potassium (mmol/24 h) | 53±24 | 62±22    | 61±21*      | 61±21*         |
| Plasma renin activity (ng/mL • h⁻¹) | 1.14 (0.74–1.66) | 0.63 (0.40–1.34)* | 0.60 (0.34–1.05)* | 0.61 (0.39–1.29)* |
| Serum aldosterone (ng/dL)   | 10.1 (7.0–13.0) | 9.6 (6.5–14.5) | 10.2 (6.7–17.6) | 10.1 (6.5–15.5) |

Values are expressed as Mean±SD or Median (Interquartile Range).

*P<0.05 vs optimal; †P<0.05 vs normal.
whereas plasma aldosterone was similar in all groups. Of note, 62% of high-normal BP group subjects had a positive family history of hypertension (ie, approximately twice the proportion observed in subjects with optimal or normal BP).

When prehypertension was considered, the proportions of male gender, positive family history of hypertension, BMI, fasting blood glucose, and urinary sodium were higher and plasma renin activity lower when compared with that of the optimal group.

Because of a significant difference in gender, BMI, and natriuresis and a trend of increasing age (all factors being important determinants of renal function and LV geometry) from optimal to high-normal BP groups, values of cardiorenal characteristics were adjusted for gender, BMI, natriuresis, and age using ANCOVA.

Renal Function

As depicted in Figure 1, GFR and filtration fraction, but not ERPF, were higher in subjects with normal and high-normal BP when compared with those with optimal BP. Of note, creatinine clearance did not allow us to detect any difference between groups (data not shown). Albuminuria expressed as μg/min or mg/mmol creatinine was similar in all groups. Consideration of prehypertension yielded the same results (ie, higher GFR and filtration fraction and similar albuminuria when compared with the optimal group).

Cardiac Parameters

As shown in Table 2, LVMI was higher in men with normal and high-normal BP when compared with men with optimal BP. No consistent change in LVMI was observed in women. RWT increased from optimal to high-normal BP group in both men and women. Midwall fractional shortening was decreased in subjects with high-normal BP, and no difference in stroke volume between groups was found. Of note, in the whole population, midwall fractional shortening was inversely correlated with LVMI ($r^2 = 0.02$, $P < 0.05$). Total arterial compliance was significantly lower in subjects with normal and high-normal BP than in subjects with optimal BP. In prehypertensive men, LVMI was higher when compared with men with optimal BP. RWT was higher in men and women in the prehypertension group, and midwall fractional shortening and total arterial compliance were lower when compared with the optimal BP group.

Using the cutoff values of LVMI found in a normotensive population (BP <140/90 mm Hg), 6% of subjects with high-normal BP (but none within the optimal group) already presented with a concentric hypertrophy. The proportion of subjects with a concentric pattern (concentric remodeling or hypertrophy) increased from 7% in the optimal BP group to 13% in the normal group and 20% in the high-normal BP group ($P < 0.05$).

**TABLE 2. Cardiac Parameters According to Blood Pressure Category**

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Normal</th>
<th>High Normal</th>
<th>Prehypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular mass index (g/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>79±2</td>
<td>82±3</td>
<td>85±3</td>
<td>84±2</td>
</tr>
<tr>
<td>Male</td>
<td>87±4</td>
<td>92±3*</td>
<td>104±2*</td>
<td>99±2*</td>
</tr>
<tr>
<td><strong>Relative wall thickness</strong></td>
<td>0.33±0.01</td>
<td>0.36±0.01</td>
<td>0.37±0.01*</td>
<td>0.37±0.01*</td>
</tr>
<tr>
<td><strong>Midwall fractional shortening (%)</strong></td>
<td>23.2±0.7</td>
<td>20.9±0.6</td>
<td>20.7±0.5*</td>
<td>20.8±0.4*</td>
</tr>
<tr>
<td><strong>Stroke volume (mL)</strong></td>
<td>78±2</td>
<td>74±2</td>
<td>76±2</td>
<td>75±1</td>
</tr>
<tr>
<td><strong>Total arterial compliance (mL/mm Hg)</strong></td>
<td>1.95±0.05</td>
<td>1.74±0.05*</td>
<td>1.69±0.04*</td>
<td>1.71±0.03*</td>
</tr>
</tbody>
</table>

Values are expressed as Mean±SEM and are adjusted for differences in age, body mass index, natriuresis, and gender using ANCOVA, except for left ventricle mass index, which is presented separately for female and male. NS indicates not significant.

* $P < 0.05$ vs optimal.
Correlation Between Cardiorenal Parameters and BP

As depicted in Figure 2, within the normotensive range of BP, LVMI was significantly correlated with casual systolic arterial pressure ($r^2=0.07$, $P<0.005$, and $r^2=0.12$, $P<0.001$ in females and males, respectively). In the whole population, RWT was also correlated with casual systolic arterial pressure ($r^2=0.08$, $P<0.005$). In contrast, no correlation between LVMI or RWT and DBP was found. Moreover, there was no correlation between albuminuria and systolic, diastolic, or mean BP. No relationship between albuminuria and LVMI or RWT was detected.

Discussion

In the present study conducted in a normotensive (ie, BP $<140/90$ mm Hg) population, it was observed that changes in renal hemodynamics and cardiac geometry are already present in subjects with normal or high-normal BP when compared with subjects with optimal BP (ie, $<120/80$ mm Hg).

In the Framingham cohort, the 10-year incidence of CV events was consistently increased in men and women independently of age at baseline in subjects with high-normal BP when compared with those with optimal BP. The present finding of a rather high ($\approx 20\%$) incidence of cardiac concentric remodeling or concentric hypertrophy may help explain the increase in CV risk found in subjects with high-normal BP. LVH is a well-known CV risk factor, independent of BP. In a population of 280 hypertensive patients followed during a mean period of 10.2 years, the incidence of CV events was higher in patients with LVH; however, the concentric pattern of LVH was associated with a markedly higher risk. The reduction in midwall fractional shortening (an index of systolic function), in subjects with high-normal BP is probably related to the increase in left ventricular mass, because in the present study LVMI was inversely correlated with midwall fractional shortening, as it has been previously described in hypertensive subjects. The increase in left ventricular mass could also contribute to the maintenance of a normal ejection fraction despite depressed myocardial performance. In hypertension, midwall fractional shortening is inversely correlated with CV morbidity and mortality, but not independently of left ventricular mass. The present finding of a correlation between SBP and LVMI and RWT suggests that BP may be the main mechanism of changes in cardiac geometry. However, because sodium intake (estimated by 24-hour natriuresis) was higher in subjects with normal or high-normal BP, a role for sodium as an amplifier of the effects of BP on the LV cannot be excluded.

In contrast to the LV, albuminuria, another marker of CV risk, did not increase from optimal to high-normal BP and no correlation between albuminuria and SBP was found. This suggests that the LV may be more sensitive than albuminuria to the increase in BP.

Although no influence of BP on albuminuria was observed, GFR progressively increased from the optimal to the high-normal level of BP, whereas no proportional modification of renal plasma flow was observed. Consequently, it is possible that the increase of GFR was maintained through an increase in filtration fraction resulting from a preferential increase in efferent arteriolar tone. The present results are in agreement with previous studies performed in prehypertensive subjects defined by the existence of a familial predisposition to hypertension. In normotensive subjects with 2 hypertensive parents, it was observed that GFR and filtration fraction were higher when compared with subjects with 2 normotensive parents. Thus, part of the results of the present study could be related to the existence of a high prevalence of familial predisposition to hypertension (62% of the subjects with high-normal BP had a positive family history of hypertension). In borderline hypertension, which can be considered as an early stage of the hypertensive disease, results are conflicting, probably because of different definitions of borderline hypertension and duration of withdrawal of antihypertensive agents. In 29 young subjects with at least 2 casual recordings of BP above 140/90 mm Hg, GFR was similar when compared with 26 normotensive (BP $<140/90$ mm Hg) controls. However, in 37 young subjects with mild essential hypertension (WHO stage I-II), glomerular hyperfiltration was reported during sympathetic nervous system activation by mental stress.

Because glomerular hypertension may be a crucial factor in the development of glomerular sclerosis, such changes in...
intrarenal hemodynamics (increase in GFR and filtration fraction) may lead to a faster decline in renal function with age in subjects with BP >120/80 mm Hg. In a recent study undertaken in approximately 100,000 subjects aged 20 to 98, Tozawa et al25 reported that within a 17-year follow-up period, the incidence of end-stage renal disease progressively increased from optimal to high-normal BP range at baseline in men and women.

In addition to the possibility of a poor autoregulation of GFR in the presence of an increase in BP in subjects with prehypertension, hormonal or metabolic factors may explain the changes in renal hemodynamics found in subjects with normal or high-normal BP. In our population, subjects with high-normal BP had the highest fasting blood glucose, which is a potential cause of glomerular hyperfiltration.26 In 10 healthy nondiabetic normotensive subjects, it was reported that an acute increase in glycemia from 4.5 to 7.2 mmol/L (hyperglycemic clamp technique) was associated with a 10% increase in insulin clearance.27

In conclusion, cardiorenal modifications are already present in subjects with normal or high-normal BP and may be related to the progressive increasing risk of CV disease found within the normotensive range of BP.3 Higher proportion of progression of BP from the normal and, more likely, high-normal BP range to sustained hypertension may be compatible with this higher CV risk. In a recent study, Vasan et al28 showed that during 4-year follow-up, the rate of progression to hypertension (BP ≥140/90 mm Hg) was 49.5% in the high-normal BP category, 25.5% in normal BP, and only 16.0% in subjects with optimal BP at baseline.

Perspectives

A consistent proportion of subjects within the normal and high-normal range of BP already have changes in left ventricular mass and geometry. The present findings of higher BMI and sodium intake in the prehypertensive group when compared with optimal BP suggest that before the use of antihypertensive agents, all efforts should be devoted to the correction of body weight and reduction in dietary sodium. Such recommendations were made in the recent JNC-75 and European Society of Hypertension–European Society of Cardiology29 guidelines. In addition, our findings may encourage us to reconsider the determination of normal values of left ventricular mass and albuminuria.

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