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Full-length article

Blood pressure, baroreflex sensitivity, and end organ damage in hybrid offspring of spontaneously hypertensive rats and Sprague-Dawley rats[1]

He-hui XIE[2], Fu-ming SHEN[2], Chao-yu MIAO, Ding-feng SU[3]

Department of Pharmacology, Second Military Medical University, Shanghai 200433, China

Key words

baroreflex; blood pressure; end organ damage; hypertension; genetic hybridization

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[2] The two authors contributed equally to this work.
[3] Correspondence to Prof Ding-feng SU.
Phn 86-21-2507-0323.
Fax 86-21-6549-3951.
E-mail dfsu@citiz.net

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Abstract

Aim: To investigate the blood pressure (BP), baroreflex sensitivity (BRS), and organ damage in hybrids of spontaneously hypertensive rats and Sprague-Dawley rats. **Methods:** Spontaneously hypertensive rats and Sprague-Dawley rats were crossbred, and the F_1 hybrids were inbred randomly to produce an F_2 generation. At the age of 52 weeks, the F_1 and F_2 hybrids were tested to determine BP and BRS in a conscious state. Histopathological examinations were carried out after BP recording and BRS studies. **Results:** BP and BRS were not different in F_1 and F_2 hybrids. BRS was inversely related to systolic BP (SBP) in male, female, or whole populations of hybrids. Quantitatively, BRS values were one-third determined by SBP level (the determinant coefficient was 0.326). The indexes for left ventricular hypertrophy, aortic hypertrophy, and renal damage were all positively related to BP, and negatively related to BRS. In multiple-regression analysis, left ventricular and aortic hypertrophy and glomerulosclerosis score were all most significantly associated with lower BRS and higher systolic BP. The contribution of BRS to left ventricular and aortic hypertrophy and glomerulosclerosis was greater than that of SBP. **Conclusion:** The present work with hybrid rats demonstrated quantitatively that the BRS value was one-third determined by SBP level. Both BP level and BRS value contributed greatly to the hypertensive organ damage. However, the contribution of BRS to the hypertensive organ damage was greater than that of BP level in these rats.

Introduction

Arterial baroreflex (ABR) plays a crucial role in cardiovascular regulation. It was found that ABR function, expressed by baroreflex sensitivity (BRS), was impaired in hypertensive patients and animals[1–4]. This impairment of BRS is attributed mainly to the high blood pressure (BP) level based on the following observations. (i) In renovascular hypertensive rats, BRS decreased significantly 1 d and 7 d after renal artery clipping[5,6]. One day after removal of a left renal artery clip, BRS was inversely related to the BP level. BRS was restored as early as renovascular hypertension was reversed[7]. (ii) In spontaneously hypertensive rats (SHR), many antihypertensive drugs lower BP and restore BRS at the same time[8,9]. On the other hand, it was found that BRS might be lower in normotensive children with hypertensive parents or in young spontaneously hypertensive rats (SHR) before hypertension[10,11]. Therefore, it is not yet clear how important BP level is in influencing BRS. To answer quantitatively this question was the first aim of the present work.

It is well known that BP level is an important determinant for end-organ damage (EOD) in hypertensive patients and hypertensive animals. However, it is certainly not the only determinant for EOD. In our previous work, it was found that BRS was related to the severity of EOD in SHR[12]. The second aim of the present work was to ascertain whether BRS was as important as BP level in determining the severity of EOD.

Hybrid offspring of SHR and normotensive rats are used widely to analyze the relationship between BP level and other

parameters. The present work was designed to study the features of BP, BRS, and EOD, and the relationships between these parameters in hybrid offspring of SHR and Sprague-Dawley (SD) rats.

Materials and methods

Animals Sprague-Dawley rats were purchased from the Sino-British SIPPR/BK Lab Animal Ltd (Shanghai, China). SHR were provided by the Animal Center of the Second Military Medical University (Shanghai, China). SHR and SD rats were crossbred, and the F_1 hybrids were inbred randomly to produce F_2 hybrids. All rats were housed at controlled temperature (23 °C–25 °C) and lighting (8:00–20:00 light: dark cycle) with free access to food and tap water. All animals used in this work received humane care in compliance with institutional animal care guidelines.

Blood pressure measurement At the age of 52 weeks, the F_1 and F_2 hybrids were tested to determine BP in a conscious state. Systolic BP (SBP), diastolic BP (DBP), and heart period (HP) were recorded continuously using techniques described previously[13,14]. The BP signal was digitized by a microcomputer. SBP, DBP, and HP values from every heartbeat were determined on line. The mean values of these parameters during a period of 24 h were calculated, and served as SBP, DBP, and HP.

Baroreflex sensitivity measurement To determine the function of ABR in conscious rats, the methods widely used are derived from that of Smyth, which was first applied to humans[15]. The principle of this method is to measure the prolongation of HP in response to an elevation of BP. With some modifications, this method has been used in conscious rats[16,17]. A bolus injection of phenylephrine was used to induce an elevation of BP. The dose of phenylephrine was adjusted to raise SBP to between 20 mmHg and 40 mmHg. HP was plotted against SBP for linear regression analysis and the slope of SBP-HP was expressed as BRS (ms/mmHg). As there exists a delay between the stimulus and response (approximately 1 s), the slopes were calculated by computer with 1–10 beats of shift for linear regression analysis, and the slope with the highest correlation coefficient was used as BRS. A correlation analysis with 5 beats of shift, for example, means that values of HP_6/SBP_1, HP_7/SBP_2, and HP_8/SBP_3 were used.

Morphological examination Morphological examinations were carried out after BP recording and BRS studies. The animals were weighed and killed by decapitation. The thoracic and peritoneal cavities were opened immediately. The right kidney, aorta, and heart were excised and rinsed in cold physiological saline. The right kidney was blotted and weighed. The left ventricle was isolated, blotted, and weighed. At the same time, the aorta was cleaned of adhering fat and connective tissue. Just below the branch of the left subclavicular artery, a 30 mm-long segment of thoracic aorta was harvested, blotted, and weighed. Ratios of left ventricular weight to body weight (LVW/BW), right ventricular weight to body weight (RVW/BW), ventricular weight to body weight (VW/BW), left ventricular weight to right ventricular weight (LVW/RVW), and aortic weight to the length of aorta (AW/length) were calculated[18,19]. Histopathological observation was also carried out using our conventional method[20]. Briefly, immediately after gross detection, all samples of left ventricles in 2 mm-thick to 3 mm-thick slices, aortae, and kidney were immersed in formalin solution for more than 1 week, dehydrated in ethanol, cleared in dimethylbenzene and embedded in paraffin. The 5 μm-thick sections were then prepared and stained with hematoxylin and eosin for light microscopic evaluation.

Glomerulosclerosis score For the semiquantitative evaluation of glomerular damage, the glomerulosclerosis score (GSS) was defined as described previously[21]. From the light microscopic specimens, approximately 50 glomeruli from the outer cortex and the same number of glomeruli from the inner cortex of each kidney were graded according to the degree of sclerosis: 0, no mesangial expansion; 1, mild mesangial expansion (less than 30% of a glomerular area); 2, moderate mesangial expansion (30%–60% of a glomerular area); 3, marked mesangial expansion (more than 60% of a glomerular area); and 4, global sclerosis. This was carried out by one observer in a blind fashion using coded slides. A weighted composite sclerosis score was then calculated for each kidney according to the following formula: glomerulosclerosis score=[1×(number of grade 1 glomeruli)+2×(number of grade 2 glomeruli)+3×(number of grade 3 glomeruli)+4×(number of grade 4 glomeruli)]×100/(number of glomeruli observed).

Statistical analysis Data were expressed as mean±SEM. Comparisons between 2 groups were made by Student's *t*-test. The relationships between hemodynamic parameters and organ damage parameters were analyzed by classic univariate correlation analysis. Stepwise multiple-regression analysis was used to study the independent effect of hemodynamic parameters on organ damage. F to enter and F to remove were set to $P<0.05$ and $P>0.10$, respectively. $P<0.05$ was considered statistically significant. Statistical analysis was carried out using software SPSS 11.0.0 (SPSS, Chicago, Illinois, USA).

Results

Blood pressure and baroreflex sensitivity in the F_1 hybrids with different parenthood Blood pressure, HP, and BRS values in the F_1 hybrids are shown in Figure 1. BP was slightly higher in H×S offspring rats (hybrids derived from male SHR and female SD rats) than in S×H offspring rats (hybrids derived from male SD and female SHR rats). This difference reached a significant level only for DBP in males and in the whole F_1 hybrid group. Male H×S rats possess significantly higher DBP than female H×S rats, but this sex difference in DBP of S×H rats was not significant. A similar sex-difference tendency was found in SBP but never reached statistical significance. No obvious sex or strain differences in HP or BRS were found in F_1 hybrids.

Blood pressure and baroreflex sensitivity in the F_1 and F_2 hybrids As shown in Figure 2, no obvious difference was found between F_1 (including H×S and S×H offspring rats) and F_2 hybrids with respect to BP, HP, and BRS. In F_1 and F_2 hybrids, male rats tended to have slightly higher BP than female rats. However, these sex differences in SBP and DBP did not reach statistical significance. The distribution of SBP and BRS in F_1 and F_2 hybrids is shown in Figure 3. No obvious difference between F_1 and F_2 was noted.

Relationship between systolic blood pressure and baroreflex sensitivity in the F_1 and F_2 hybrids It was found that BRS was significantly and inversely related to SBP in both F_1 (r=-0.599, n=96, P<0.01) and F_2 offspring (r=-0.510, n=36, P<0.01) (Figure 4A,4B). When the whole population (F_1+ F_2) were analyzed, the correlation coefficient (r) was -0.571 (n=132, P<0.01) (Figure 4C) and the determinant coefficient (r^2) was 0.326. This value means that the BRS value is 33% determined by SBP level. In accordance with this result, it was found that lower BRS was not always linked to higher BP in the hybrid offspring rats. In the hybrids studied (Figure 4), we found some normotensive animals with a lower BRS (SBP<140 mmHg, BRS<0.4 ms/mmHg; n=5) and hypertensive animals with a higher BRS (SBP>150 mmHg, BRS>0.7 ms/mmHg; n=22). Two examples for BRS obtained from the hybrids are shown in Figure 5A, a normotensive animal with a lower BRS; and Figure 5B, a hypertensive animal with a higher BRS.

Organ damage in the F_1 and F_2 hybrids The average values of LVW/BW, AW/length, and GSS are presented in Figure 6. No obvious difference between F_1 and F_2 hybrids was found.

Relationships between blood pressure, baroreflex sensitivity, and organ damage in hybrids The relationships between BP, HP, BRS, and organ damage in the hybrids were shown in Table 1. It was found that LVW/BW, an index for left ventricular hypertrophy, AW/length, an index for aortic hypertrophy, and GSS, an index for renal damage, were all

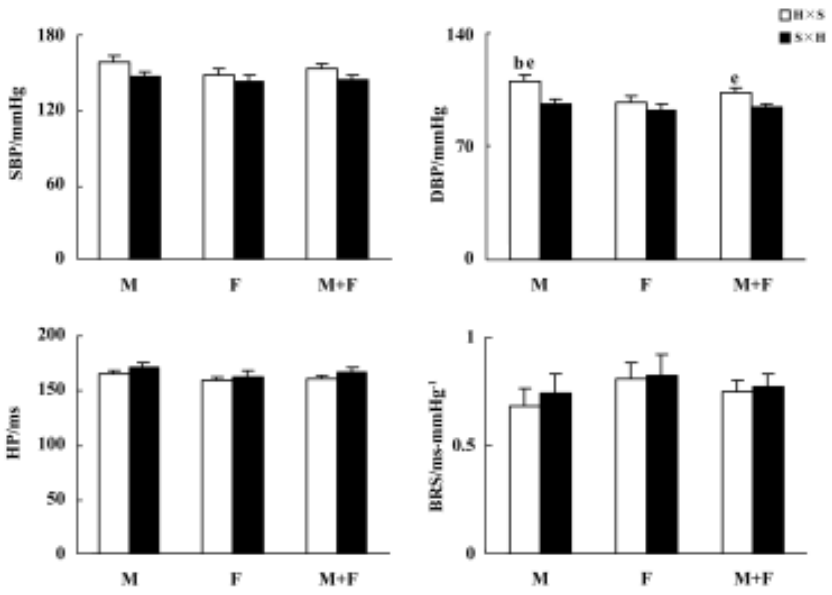

Figure 1. Blood pressure (BP), heart period (HP) and baroreflex sensitivity (BRS) in the F_1 hybrids with different parenthood. BRS, baroreflex sensitivity; DBP, diastolic blood pressure; H×S, hybrids derived from male spontaneously hypertensive rats (SHR) and female Sprague-Dawley (SD) rats; SBP, systolic blood pressure; S×H, hybrids derived from male SD rats and female SHR. The numbers of rats used were 24 and 25 in male (M), 29 and 18 in female (F), and 53 and 43 in total (M+F) H×S and S×H rats, respectively. ^bP<0.05 *vs* female H×S. ^eP< 0.05 *vs* corresponding S×H strain.

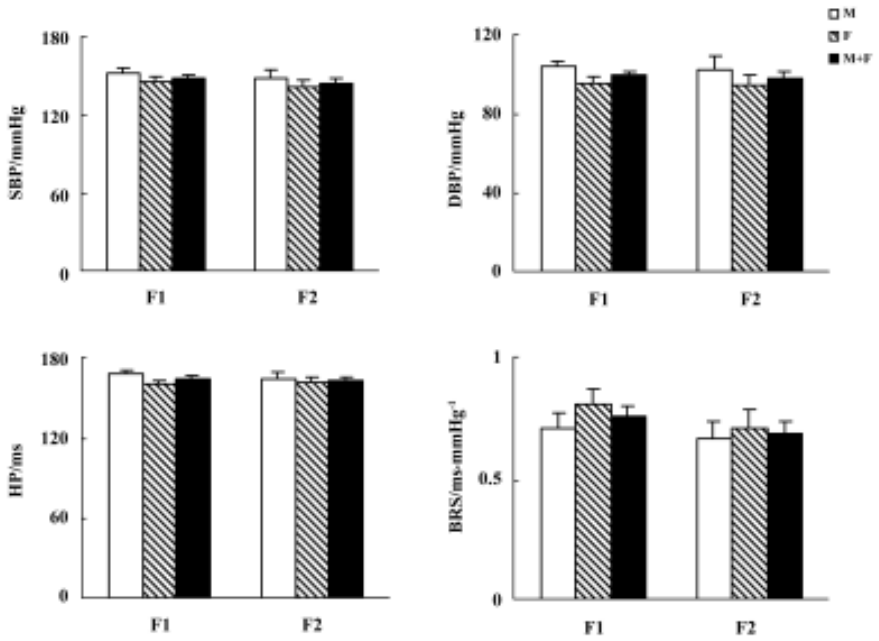

Figure 2. Blood pressure (BP), heart period (HP), and baroreflex sensitivity (BRS) in the F_1 and F_2 hybrids. See Figure 1 for abbreviations. The numbers of rats used were 49 and 16 in male (M), 47 and 20 in female (F), and 96 and 36 in total (M+F) F_1 and F_2 hybrids, respectively.

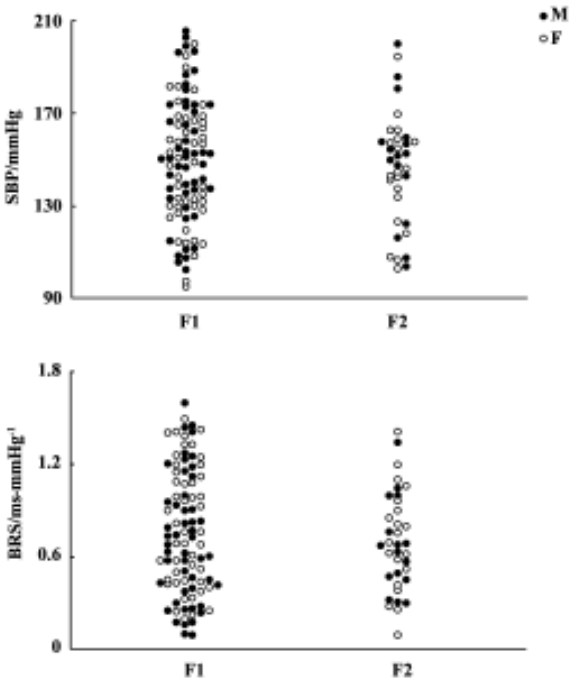

Figure 3. The distribution of systolic blood pressure (SBP) and baroreflex sensitivity (BRS) in the F_1 and F_2 hybrids. See Figure 1 for abbreviations. The numbers of rats used were 49 and 16 in male (M), and 47 and 20 in female (F) F_1 and F_2 hybrids, respectively.

related positively to BP, and related negatively to BRS. There was no significant relationship between HP and organ damage parameters (Table 1). Some examples for important correlations were shown in Figure 7.

Table 1. Linear regression coefficient (*r*) between blood pressure (BP), heart period (HP) and baroreflex sensitivity (BRS) values and organ damage in hybrids. n=132. ^cP<0.01.

	LVW/BW	AW/length	GSS
SBP	0.492^c	0.464^c	0.465^c
DBP	0.416^c	0.303^c	0.411^c
HP	-0.162	-0.074	-0.164
BRS	-0.646^c	-0.559^c	-0.590^c

AW, aortic weight; BW, body weight; DBP, diastolic blood pressure; GSS, glomerulosclerosis score; LVW, left ventricular weight; SBP, systolic blood pressure.

The relative dependencies of organ damage on hemodynamic parameters were assessed by stepwise multiple-regression analysis. LVW/BW, AW/length, and glomerulosclerosis score were all most significantly associated with lower BRS (β=-0.542, P<0.01; β=-0.436, P<0.01; and β=-0.482, P<0.01, respectively) and higher SBP (β=0.183, P<0.01; β=0.216, P<0.01; and β=0.191, P<0.01, respectively). After comparing the standardized partial regressive coefficients, it was found that the contribution of BRS to left ventricular, aortic hypertrophy, and glomerulosclerosis was greater than

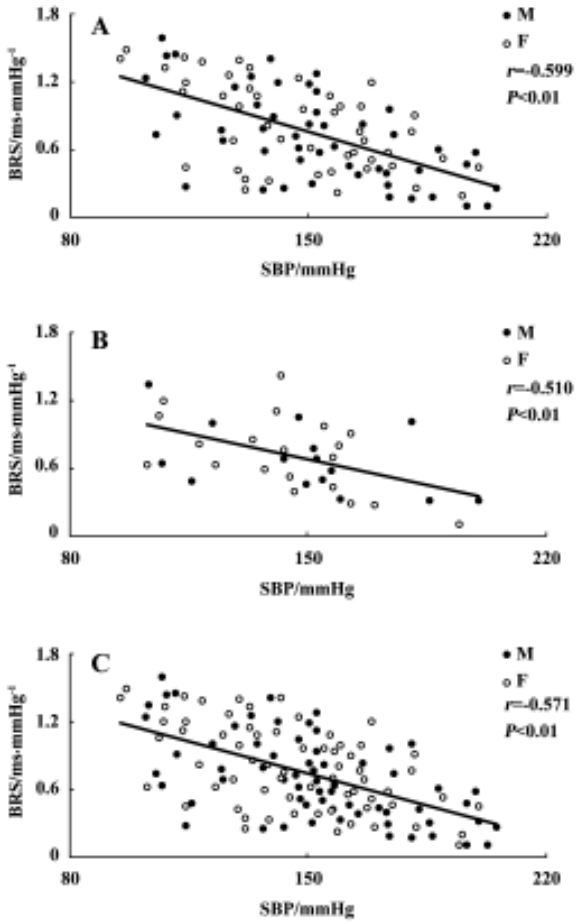

Figure 4. Correlation between blood pressure (SBP) and baroreflex sensitivity (BRS) in the F_1, F_2, and F_1+F_2 hybrids. See Figure 1 for abbreviations. The numbers of male (M) and female (F) rats used were 49 and 47, 16 and 20, and 65 and 67 in F_1 (A), F_2 (B), and F_1 + F_2 (C) hybrids, respectively.

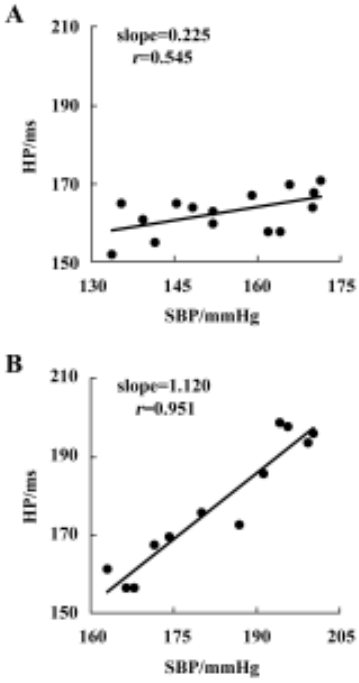

Figure 5. Schematic presentation of baroreflex sensitivity obtained from the hybrids. See Figure 1 for abbreviations. (A) A normotensive rat with lower baroreflex sensitivity. (B) A hypertensive rat with normal baroreflex sensitivity. Slope of the regression is expressed as baroreflex sensitivity.

that of SBP.

Discussion

The main contributions of the present work may be summarized as follows:

(i) It is well known that the BRS value is closely related to and importantly determined by BP level. The present work is the first to demonstrate quantitatively that BRS value is one-third determined by SBP level (the determinant coefficient was 0.326).

(ii) Both BRS and SBP level contributed to organ damage. This report is the first to show that the contribution of BRS to organ damage is greater than that of SBP.

(iii) F_1 hybrid offspring are suitable for studying the relationships between BP level and other parameters.

Many abnormalities or changes have been reported to relate to high BP level in hypertension. Among these abnormalities or changes, some are intrinsically related to hypertension and some are only accompanying phenomena in hypertension. Hybrid offspring of hypertensive and normotensive rats are often used to distinguish these 2 sorts of changes found in hypertension. Using these hybrid offspring, it was found that the genes responsible for the hypertensive trait and those responsible for the hyperactivity trait are not tightly linked[22,23]. The relationships between BP and other parameters, such as salt appetite[24], temperature[25], and sensitivity to stress[26], have also been studied in the hybrids rats derived from hypertensive and normotensive rats. Recently, hybrid rats derived from a hypertensive and normotensive strain were produced to study genetic markers for blood pressure using statistical techniques for quantitative trait loci analysis[27]. It has been noted that BRS is lower in hypertensive patients and hypertensive animals. However, no study has been carried out using hybrid rats to analyze the relationship between BP and BRS. This may be due to the large quantity of work that it entails; the measurement of BRS in conscious and unrestrained rats requires a computerized BP monitoring system and more than 100 rats are

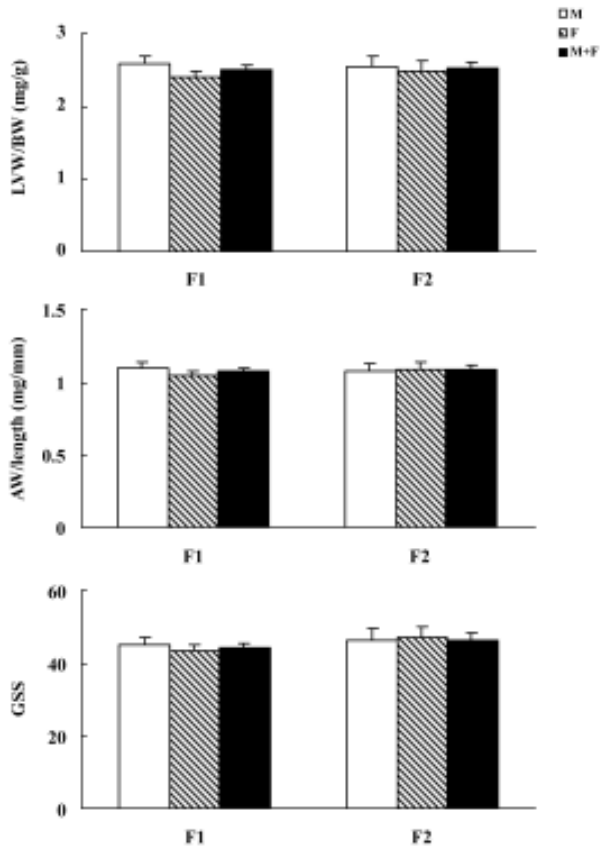

Figure 6. Organ damage in the F_1 and F_2 hybrids. AW, aortic weight; BW, body weight; GSS, glomerulosclerosis score; LVW, left ventricular weight. The numbers of rats used were 49 and 16 in male (M), 47 and 20 in female (F), and 96 and 36 in total (M+F) F_1 and F_2 rats, respectively.

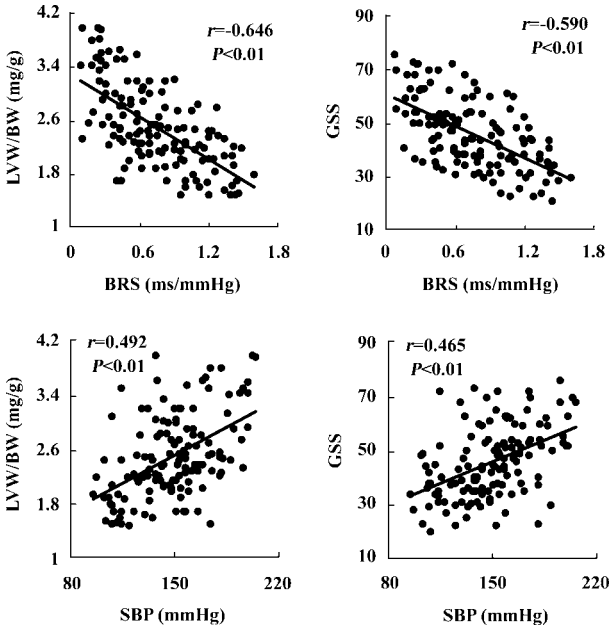

Figure 7. Examples of the correlation between hemodynamic parameters and organ damage parameters in hybrids. n=132. See Table 1 for abbreviations.

needed for such a study. Investigating the relationship between BP and BRS using hybrid offspring rats was the first aim of the present work.

To analyze the links between BP and other parameters previous studies have used hybrid rats derived from a cross between SHR and Wistar-Kyoto (WKY) rats[22–26], stroke-prone SHR (SHRSP) and WKY rats[28], Dahl/Iwai salt-sensitive rats and WKY rats[29], New Zealand genetically hypertensive rats and Wistar rats[23], and SHR and Donryu rats[30]. In the present study, SHR were crossbred with SD rats, but not with WKY rats. This is based on the following considerations: (i) WKY rats possess a relatively higher BP level than SD rats; and (ii) compared with WKY rats, the genetic background of SD rats is more different from that of SHR. Therefore, using SD rats may help to produce hybrid rats exhibiting wider range of BP levels or BRS values, which would be expected for the correlation analysis.

It was found in previous studies that the BP of hybrid offspring derived from SHR and WKY rats depended on the strain of the male progenitor of the cross; male offspring with an SHR male progenitor had significantly higher BP (SBP, +20 mmHg) than male offspring with a WKY male progenitor[31]. The same results were also found in hybrids of SHRSP and WKY rats (SBP/DBP, +20/15 mmHg)[28]. These observations showed strong evidence for a locus or loci on the SHR or SHRSP Y chromosome that contributed to hypertension in these models. Some subsequent studies confirmed the Y-chromosome effect on BP[27,32]. In accordance with previous reports, the current work showed that the male F_1 hybrids with hypertensive fathers had higher BP levels than those with normotensive fathers (SBP/DBP, +12/14 mmHg). The difference reached a significant level only for DBP. These differences found in the present work were slightly lower than those in previous studies. This might be due to the difference in BP measurement: we measured BP continuously for 24 h while others measured BP either once by tail sphygmomanometry[31] or by using average values sampled every 5 min for 10 s over a 4 d period using the radiotelemetry system[28]. However, in our study, the F_1 hybrids with different parenthood had similar HP and BRS values.

In previous studies concerning hybrid offspring rats, F_1, F_2 or the whole population of F_1 and F_2 were used[22–26,30]. The use of F_2 hybrids is based on the expectation of obtaining a wider distribution range in the parameters studied. In the present work, no obvious differences in the average val-

ues of SBP and BRS were found between F_1 and F_2 hybrids. In addition, the distribution of SBP and BRS values was similar in F_1 and F_2 hybrids. It is known that BP and BRS phenotypes are not controlled by only one gene, but rather by many genes[27]. This may explain the wide distribution range of SBP and BRS values. Accordingly, we propose that F_1 hybrids may be suitable for these kinds of studies.

Abnormalities in baroreflex have been demonstrated in numerous studies in both experimental and human hypertension[15,33], and the impairment in baroreflex is thought to be the result of elevated BP or reduced arterial distensibility[6,7]. In agreement with previous studies, we found that BRS was significantly and inversely related to SBP in the hybrid offspring rats. However, in the hybrids studied, we also found some normotensive animals with a lower BRS and hypertensive animals with a higher BRS. These results indicate that lower BRS is not always linked to higher blood pressure in the hybrid offspring rats. Previous studies have shown that impairment of BRS may be present early in the course of, or may precede the development of, hypertension. BRS has been shown to be diminished in the early phase of hypertension in SHR as well as in borderline essential hypertension in humans; impairment of BRS is thought to be genetically determined in part[10,34]. In addition, it was found that other factors, such as alterations in endothelial prostaglandins and opioid peptides, might also contribute to the impairment of BRS[35,36]. Therefore, BP is not the only determinant of BRS. However, it is not clear how important BP level is in influencing BRS. Our study, for the first time, demonstrated quantitatively that BRS was one-third determined by SBP level (the determinant coefficient was 0.326).

It is well known that high BP level induces organ damage, while decreasing BP level can prevent EOD. Our present study showed that both SBP and DBP were significantly and positively related to LVW/BW, AW/length, and GSS. These results indicate that elevated BP has a major effect on EOD in hybrid offspring rats. However, BP level is not the only determinant for EOD. Our previous study proposed that BRS was one of the independent variables related to EOD score [12]. In the present work, BRS was significantly and negatively related to LVW/BW, AW/length, and GSS. Multiple-regression analysis showed that the contribution of BRS to left ventricular, aortic hypertrophy, and glomerulosclerosis was greater than that of SBP. The present study is the first to show that BRS makes a greater contribution to hypertensive organ damage than does BP level.

In conclusion, the present work with hybrid rats demonstrated quantitatively that BRS value was one-third determined by SBP level. Both BP level and BRS value contributed to the hypertensive organ damage. However, the contribution of BRS to the hypertensive organ damage was greater than that of BP level in these rats.

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