

Genetic Influences on Baroreflex Function in Normal Twins

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Abstract—Blood pressure and heart rate are strongly influenced by genetic factors; however, despite the pivotal role of genetics in short-term cardiovascular regulation, little is known about the genetic contribution to baroreflex function. We assessed genetic influence on baroreflex sensitivity (BRS) in 149 twin pairs (88 monozygotic of age 33 ± 13 years and BMI 23 ± 4 kg/m² and 61 dizygotic of age 33 ± 11 years and BMI 24 ± 4 kg/m²). ECG and finger arterial blood pressures were measured continuously under resting conditions. BRS values were calculated by use of cross-spectral analysis (baroreflex slope calculated as mean value of transfer function between systolic blood pressure and the R-R interval in the low-frequency band [BRSLF] and baroreflex slope calculated as the mean value of transfer function between systolic blood pressure and R-R interval in the respiratory frequency band [BRSHF]) and the sequence technique (BRS+, BRS-). Heritability (h^2) was estimated with a path-modeling approach. BRS values did not differ significantly between groups (monozygotic, BRSLF, 17 ± 13 ; BRSHF, 21 ± 18 ; BRS+, 19 ± 16 ; and BRS-, 21 ± 15 , and dizygotic, BRSLF, 16 ± 9 ; BRSHF, 20 ± 14 ; BRS+, 18 ± 10 ; and BRS-, 20 ± 11 ms/mm Hg), and were significantly correlated ($P < 0.001$). When variances and covariances for monozygotic and dizygotic twins were compared, significant correlations were found for BRS in monozygotic (range, $r = 0.38$ to 0.48) but not in dizygotic twin pairs ($r = -0.03$ to 0.09). Thus, BRS is heritable; the variability can be explained by genetic influences ($P < 0.01$; h^2 range, 0.36 to 0.44). The genetic influence on BRS remained strong after correction for BMI and blood pressure. Therefore, BRS is strongly genetically determined, probably by different genes than are resting blood pressure and BMI. (*Hypertension*. 2001;37:907-910.)

Key Words: blood pressure ■ function, autonomic ■ analysis, spectral ■ baroreflex ■ twins ■ genetics

The baroreflexes play a pivotal role in short-term blood pressure (BP) and heart rate regulation.¹ Carotid and aortic baroreceptors sense changes in stretch that result from BP alterations.^{2,3} The signal generated in these receptors travels to cardiovascular control centers in the brain stem. This afferent input results in counterregulatory adjustments of sympathetic and parasympathetic tone and prevents excessive fluctuations in BP. Interruption of the afferent arc (baroreflex failure) or the efferent arc (autonomic failure) is associated with extremely labile BP and heart rate.^{4,5} Considering the profound effect of complete baroreflex dysfunction on BP and heart rate, even mild abnormalities in baroreflex function could result in substantial changes in cardiovascular regulation. Several studies suggested that baroreflex abnormalities are an important contributing factor to the pathogenesis of arterial hypertension.^{1,6-10} Baroreflex disturbances are associated with increased cardiovascular morbidity and mortality.¹¹ Thus, defining the mechanisms that affect baroreflex function could have an important effect on our understanding of cardiovascular diseases.⁷ Recent studies suggested that baroreflex function is influenced by genetic factors.^{7,12,13} However, the magnitude of the genetic contribution to baroreflex function is not known. We estimated the magnitude of

the genetic effect on baroreflex function in a cohort of normal twins. We tested whether baroreflex sensitivity is influenced by different genes than resting BP and body mass index (BMI), which are known to influence baroreflex function.

Methods

Subjects

We investigated the heritability of baroreflex sensitivity in 149 twin pairs (88 monozygotic and 61 dizygotic). Twin pairs were recruited by advertisement in public print media. All of these normal German twin pairs underwent a medical history taking and physical examination before the study. Persons on ingested medications were excluded from study. Hours of vigorous physical activity per week were estimated by questionnaire. Zygosity was determined by use of 5 microsatellite markers coamplified by polymerase chain reaction. Written informed consent was obtained before study entry as required by the institutional review board.

Study Protocol

Studies were conducted in a quiet room at 20°C during morning hours with the subject in a semi-supine body position. Five-minute recordings were obtained after 10 minutes of rest. BP was measured in the nondominant arm by automated oscillometric device (Dinamap) as well as continuously by Finapres (Ohmeda) BP monitor attached to the middle finger of the right hand. The subject's right

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hand was kept at heart level. ECG was recorded continuously with a modified standard lead to optimize the R peak. Respiratory activity was obtained with a pneumobelt. Data were analog-digital converted (ECG 1 kHz, BP 100 Hz). Peak detection (R peak, systolic BP [SBP] and diastolic BP) was realized offline with PV-wave software (VisualNumerics).

Baroreflex-Sequence Technique

Spontaneous baroreflex slope (BRS) was calculated as slope of the linear regression lines between SBP and the subsequent R-R intervals (within the same or the next heart beat) values by use of the sequence technique. Sequences with ≥ 3 intervals, 0.5-mm Hg BP changes, and 5-ms R-R interval changes were analyzed only if correlation coefficients were >0.85 . BRS was calculated as mean value of significant slopes obtained.

Baroreflex-Cross-Spectral Analysis

Power spectral analysis has provided useful information about the temporal fluctuations of different hemodynamic parameters, such as heart rate variability.¹⁴ Cross spectra are used to capture interrelationships between parameters in the time and frequency domain. Therefore, we calculated the power spectra of SBP and R-R interval time series with fast Fourier transformation (segment length, 256 s; resampling with 4 Hz; resolution, 0.004 Hz) and the cross spectra.¹⁵ Baroreflex gain was determined to be the mean value of the transfer function in the low- and high-frequency bands. BRS was considered significant if the coherence in the analyzed frequency band was >0.8 .

Statistics and Quantitative Genetics

Statistical analysis was conducted by use of the SPSS program. All data are expressed as mean \pm SD. Relationship between parameters was assessed by linear regression analysis. Interindividual differences of mean group values were tested with unpaired *t* test. A value for $P < 0.05$ was considered to be statistically significant. Parameters of the quantitative genetic models were estimated by structural equation modeling by use of the MX program developed by Neale.¹⁶ Variability of any given phenotype within a population can be decomposed into genetic influences (VaraddGen), environmental influences shared by the twins within a family (VarsharedEnv) and effects of random environment (Varenv), as follows:

$$\text{Var} = \text{VaraddGen} + \text{VarsharedEnv} + \text{Varenv.}$$

For MZ and DZ, the covariance of their phenotype is given by:

$$\text{CovMZ} = \text{VaraddGen} + \text{VarsharedEnv};$$

$$\text{CovDZ} = 0.5 \text{ VaraddGen} + \text{VarsharedEnv}.$$

Heritability analysis in twin studies can estimate additive components of genetic variability as well as two environmental influences, shared and nonshared environmental influences.¹⁷ These values estimate the relative amount of the influence of the variable on interindividual differences up to a sum of 1. Genetic and environ-

TABLE 1. Demographic Data of the Twin Pairs

Parameter	Twins	
	Monozygotic	Dizygotic
No.	176	122
Age, y	33 \pm 13	33 \pm 11
Gender (F/M), n	116/60	82/40
Height, cm	169 \pm 9	170 \pm 9
Weight, kg	67 \pm 11	70 \pm 15
BMI, kg/m ²	23.0 \pm 3.5	23.8 \pm 4.0
SBP, mm Hg	125 \pm 16	123 \pm 13
DBP, mm Hg	72 \pm 11	73 \pm 10
Heart rate, bpm	71 \pm 11	69 \pm 12

Values are mean \pm SD.

TABLE 2. Group Mean Values of Baroreflex Slopes for Monozygotic and Dizygotic Twins Estimated With Cross-Spectral Analysis and Sequence Technique

Parameter	Twins	
	Monozygotic	Dizygotic
BRS _{LF}	17 \pm 13	16 \pm 9
BRS _{HF}	21 \pm 18	20 \pm 14
BRS+	19 \pm 16	18 \pm 10
BRS-	21 \pm 15	20 \pm 11

Values are mean \pm SD.

mental effects were estimated by the best-fit model as selected by χ^2 value. Adjustments of baroreflex slopes for age, BMI, and BP were done by multiple linear regression with unstandardized residuals. In case of significant deviations from normal distribution, appropriate transformations were applied.

Results

Monozygotic and dizygotic twins had similar age, BMI, resting BP, and resting heart rate (Table 1). Baroreflex slopes (Table 2) determined with different methods were highly correlated (Figure 1). Large interindividual variability existed in baroreflex sensitivity. For example, baroreflex slopes determined by the sequence technique ranged from 2 to 82 ms/mm Hg. Baroreflex slopes determined with sequence and cross-spectral techniques were similar in monozygotic and dizygotic twins. A significant decrease was seen in baroreflex sensitivity with age (Figure 2). Distribution of baroreflex sensitivities resembled the pattern described earlier in normal subjects of similar age.¹⁸ Baroreflex sensitivity was negatively correlated with BMI and resting BP. Daily physical activity was positively correlated with baroreflex sensitivity (Table 3). No gender differences occurred in baroreflex sensitivity.

Baroreflex sensitivity was significantly correlated in monozygotic twin pairs but not in dizygotic twin pairs (Table 4). Because age had a strong effect on baroreflex sensitivity, baroreflex sensitivities were adjusted for age for heritability analysis. Heritability of baroreflex sensitivity adjusted for age ranged from 0.36 to 0.44. These results suggest a strong genetic influence on baroreflex sensitivity. Heritability of baroreflex sensitivity deter-

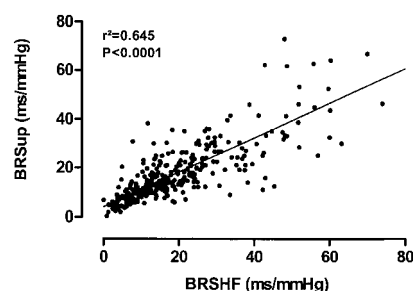


Figure 1. Linear regression analysis between baroreflex sensitivity determined by different methods. BRS_{Sup} indicates baroreflex slope calculated by use of the sequence technique for increasing SBP; BRS_{HF}, baroreflex slope calculated as mean value of the transfer function between SBP and the R-R interval in the respiratory-frequency band (0.15 to 0.4 Hz).

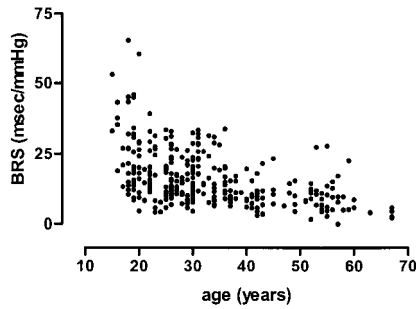


Figure 2. Baroreflex sensitivity as a function of age. BRSLF indicates baroreflex slope calculated as mean value of the transfer function between SBP and the R-R interval in the low-frequency band (0.04 to 0.15 Hz).

mined by cross-spectral analysis and sequence technique (upslopes) was attenuated only slightly after adjustment for BMI and resting BP. Heritability of BRS determined by sequence technique with downslopes was markedly reduced after adjustment for BMI and resting BP.

Discussion

The main finding of the present study is that BRS in the normal human is strongly influenced by genetic variance. The heritability estimate was only slightly attenuated after correction for BMI and BP. Therefore, BRS seems, in part, to be influenced by different genes than are resting BP and BMI. This finding is of potential clinical relevance because abnormalities in BRS have been implicated in the pathogenesis of arterial hypertension and are associated with increased cardiovascular mortality.^{1,6–11}

Few human studies have addressed the issue of whether baroreflex function is influenced by genetic factors. None of these studies provided estimates of the magnitude of the genetic effect on BRS. For example, normotensive and borderline hypertensive subjects with a family history of hypertension exhibited a decrease in BRS compared with normotensives without a family history of hypertension.¹⁹ In one population-based study from Finland, a common genetic polymorphism in the promoter and in the coding region of the aldosterone-synthase gene was found to influence baroreflex sensitivity.²⁰ This effect appeared to be stronger in younger than in older subjects. In contrast, no association was found for BRS with insertion/deletion polymorphism of the angiotensin-converting enzyme gene or M235T variants of the angiotensinogen gene. The hypothesis that the renin-angiotensin-aldosterone system contributes to BRS is supported by the observation that BRS can be improved with angiotensin-converting enzyme inhibition.¹⁸ The effect of numerous genes

TABLE 3. Cross Correlation Between BRSLF, BMI, BP, and Physical Activity

Parameters	r ² (Pearson)	P
BRSLF vs BMI	-0.193	<0.001
BRSLF vs SBP	-0.335	<0.001
BRSLF vs DBP	-0.319	<0.001
BRSLF vs Physical Activity	0.166	<0.02

TABLE 4. Intraclass Correlation Coefficients (r) and Heritability (h²) for Monozygotic and Dizygotic Twins Before and After Correction for BMI and Resting BP (c) for Calculated Baroreflex Slopes

Parameter	r MZ	r DZ	h ²	r MZc	r DZc	h ² c
BRSLF	0.48	0.05	0.43*	0.43	0.13	0.41*
BRSHF	0.44	-0.03	0.40*	0.37	0.08	0.35*
BRS+	0.46	0.03	0.42*	0.40	0.16	0.39*
BRS-	0.38	0.09	0.36*	0.29	0.20	0.18

MZ indicates monozygotic; DZ, dizygotic twins.
*P<0.01.

on BRS was studied in animals.^{21–24} These genes are possible candidate genes for future studies in humans.

We assessed only the genetic contribution to baroreflex control of heart rate. Baroreflex control of heart rate is mainly achieved through changes in parasympathetic tone. In contrast, baroreflex control of vascular tone is a function of the sympathetic nervous system.^{1,13,15} Changes in baroreflex control of heart rate are not always associated with similar changes in regulation of vascular tone.^{13,25} Thus, the results of the present study cannot be interpreted to indicate a genetic effect on vascular tone exercised by the sympathetic nervous system. The genetic effect on parasympathetic and on sympathetic regulation by the baroreflex could be independent, in part.^{25–27} Yet, in an earlier study, family history of hypertension was associated with attenuated baroreflex-mediated reduction in sympathetic nerve traffic.¹³ An interesting case report described a symptomatic failure of the baroreceptor BP buffering mechanism in a woman with familial aniridia. Her baroreceptor cardiac inhibition was intact.²⁵ Furthermore, the parasympathetic component of the arterial baroreflex becomes impaired with advancing age. Baroreflex control of sympathetic outflow to the peripheral circulation, as assessed by direct measurements of muscle sympathetic nerve activity, can be well maintained in healthy individuals even into the seventh decade of life.²⁷

Characterization of the baroreflex control of sympathetic outflow in large-scale genetic studies will be difficult because direct measurement of muscle sympathetic nerve activity is complicated, involves intravenous infusions of vasoactive medications, and is established at only a few centers. From a clinical standpoint, characterization of the genes that influence baroreflex control of heart rate may be more urgently needed because of the wealth of data implicating BRS as a prognostic marker.¹¹

Twin studies have been extensively used to characterize the interaction of genetic and environmental factors on cardiovascular phenotypes.²⁸ The twin approach allows detection and quantification of genetic effects in relatively small subject groups.¹⁷ One potential limitation of the present study is that we characterized genetics of baroreflex function in a cohort of healthy subjects. However, genes involved in monogenic diseases were shown to act as quantitative trait loci in the general population, which supports the close relationship between physiological and pathological processes.^{29,30} Thus, the genetic effect on BRS also may be important in the pathogenesis of cardiovascular disorders. These genetic

factors may modulate the effect of aging, BMI, physical activity, and BP on baroreflex function. Baroreflex slope calculated as the mean value of the transfer function between SBP and the R-R interval in the low-frequency band, baroreflex slope calculated as the mean value of the transfer function between SBP and the R-R interval in the respiratory-frequency band, and BRS+ showed strong evidence for heritability. When corrections for resting BP and BMI were made, the same degree of heritability was still evident. Only the heritability estimated for BRS- was attenuated after adjustment for BMI and resting BP. These findings support the interpretation that BRS is controlled by distinct genetic factors independent of those influencing BMI and resting BP.

We conclude that BRS is strongly influenced by genetic factors. BRS seems to be, at least in part, influenced by different genes than BMI and resting BP. BRS may thus be an important additional intermediate phenotype in genetic studies on cardiovascular regulation. Furthermore, elucidation of the genes influencing BRS may provide new insight into cardiovascular regulation and pathogenesis of cardiovascular diseases.

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