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Abstract—The present study estimated the genetic influences on ambulatory systolic and diastolic blood pressure, and on hypertensive status derived from ambulatory levels, in a family sample of 535 twins and 257 singleton siblings. This "extended twin design" was used to explicitly test the possibility that results obtained in singleton siblings are different from those obtained in twins. To examine the effects of excluding (medicated) hypertensive subjects, the genetic analyses were first performed under strict exclusion (medication and/or blood pressure >135/85 mm Hg), then without the medicated subjects, and, finally, without any exclusion. For the latter analysis, the untreated blood pressure values in subjects using antihypertensive medication were estimated by augmenting the observed blood pressure by the published efficacy of the specific antihypertensive medication used. No evidence was found for differential means, variances, or covariances of ambulatory blood pressure in singletons compared with twins. This indicates that estimates of heritability of ambulatory blood pressure from twin studies can be generalized to the singleton population. Heritability of hypertension, defined as a mean daytime blood pressure >135/85 mm Hg or antihypertensive medication use, was 61%. Genetic contribution to ambulatory blood pressure was highest when all subjects were included (systolic, 44% to 57%; diastolic, 46% to 63%) and lowest under strict exclusion (systolic, 32% to 50%; diastolic, 31% to 55%). We conclude that exclusion of (medicated) hypertensives removes part of the true genetic variance in ambulatory blood pressure. **(*Hypertension*. 2005;45:80-85.)**

Key Words: blood pressure monitoring ■ hypertension, genetic ■ antihypertensive agents ■ genetics ■ twins

A large number of twin and family studies have shown significant genetic contributions to individual differences in blood pressure (BP).[1–5] Most of these studies have based their genetic analyses on conventional office BP measurements. The genetics of ambulatory BP (ABP) may differ, however, because it is unaffected by the "white-coat" effect.[6] The added value of ABP measurements is best illustrated by studies showing that ABP is a better predictor of target organ damage,[7] cardiovascular morbidity, and mortality[8,9] than conventional office BP.

To date, only 4 twin studies[10–13] and 1 family study[14] reported heritability estimates for daytime or 24-hour ABP. Estimates ranged from 22% to 62% for systolic blood pressure (SBP) and from 38% to 63% for diastolic blood pressure (DBP). With the exception of studies by Vinck et al[12] and Fagard et al,[13] sample sizes for the twin analyses have been rather small, ie, at most, 66 pairs in total. Thus, there is a relative paucity of adequately powered twin studies on ambulatory measures. One way of increasing statistical power is to include singleton siblings. Such an extended twin design[15] further provides an optimal design to address the question whether results from twin studies on the genetics of ABP may be generalized to the singleton population, because it matches twins and singletons for familial factors like socioeconomic status (SES), diet habits, and maternal behaviors during pregnancy.

Existing twin and family studies of ABP have excluded subjects using antihypertensive medication,[12,13] or have been performed with analyses of normotensive subjects only,[10,11] thereby removing an important part of the population variance of interest.[16] The present study estimated the genetic influences on hypertensive status and ambulatory SBP and DBP in a large sample of twins and their singleton siblings. To examine the effects of exclusion, the genetic analyses on ABP were first performed on normotensive subjects only, secondly after exclusion of medicated hypertensive subjects, and finally without any exclusion.

Methods

Subjects

The study sample was composed of 230 monozygotic (MZ) twins (85 men), 305 dizygotic (DZ) twins (111 men), and 257 singleton siblings (98 men) from 339 families, all registered in the Netherlands Twin Register (NTR). Their average age was 31.3 (SD 11.2) years.

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TABLE 1. Model Fitting Results for Hypertension

Model	$\Delta\chi^2$	Δdf	*P*	AIC	A, %	C, %	E, %
ACE	—	—	—	—	61 (0–83)	0 (0–49)	39 (17–75)
AE	0	1	1.000	−2.000	61 (33–83)	—	39 (17–67)
CE	2.355	1	0.125	0.356	—	37 (18–56)	63 (44–82)
E	18.914	2	0.000	14.914	—	—	100

Shown are $\Delta\chi^2$ values and gain in degrees of freedom of the models and accompanying estimates for additive genetic (A) and shared (C) and unique environmental (E) influences.

AIC indicates Akaike information criterion.

The 95% confidence intervals are given in parentheses.

Zygosity of the twins was determined by DNA typing. The Ethics Committee of the Vrije Universiteit approved of the study protocol, and all subjects gave written consent before entering the study. No payment was made for participation, but all subjects received an annotated review of their BP recording.

Procedures

Subjects were visited in the morning before going to work and were requested to refrain from intense physical activity on the preceding and the ambulatory monitoring days. A Spacelabs 90207 ABP monitor (Redmont, Wash) and an ambulatory ECG/ICG recorder,[17] which includes a vertical accelerometer, were attached to the subject and the operation was explained. Arm circumference was measured to choose the appropriate arm-cuff size. BP measurements were initiated automatically every 30 minutes. Before inflating, the device gave an auditory 2-tone beep to warn participants to keep their arm as still and relaxed as possible. Subjects were unable to observe their own BP readings. The monitor was programmed to retake a measurement 2 minutes after a misreading. Every 30 (±10) minutes, subjects were prompted by an auditory beep to write down a chronological account of activity (eg, deskwork, housekeeping, watching TV), posture (lying, sitting, standing, walking, and bicycling), and location (eg, at home, at work, at a public place). When they went to bed, participants removed the BP monitor. The signal from the vertical accelerometer was combined with the diary information to check the diary entries on posture and physical activity for accuracy.

Data Reduction

Previous recommendations for excluding artifacts and outliers from ambulatory recordings were followed.[18] The reported times of diner and lunch, awakening, and bedtime were used to compute mean SBP and DBP across all readings in the morning, afternoon, and evening. To assess the confounding of different physical activity patterns on ABP levels, we also computed the average ABP on the 3 periods of the day using only BP values obtained during sitting activities. Applying European Society of Hypertension criteria, hypertension was considered present when subjects were currently using prescribed antihypertensive medication or when mean daytime ABP was higher than 135/85 mm Hg.[19]

Statistical Analysis

Heritability estimates of hypertension and daytime ABP were obtained from structural equation modeling of the MZ and DZ/sib variances and covariances using the structural equation program Mx.[20] Hypertension heritability was assessed using a liability–threshold model, which assumes a latent, normally distributed liability to disease that is manifest as a categorical phenotype.[21] For ABP, the best-fitting trivariate model was used to estimate the relative contribution of genetic and environmental influences to the variance of the 3 daytime period means of SBP and DBP. A detailed description of the model-fitting procedures is found in the online supplement available at http://www.hypertensionaha.org.

These analyses on ABP were performed 3 times, in 3 different sets of subjects. In the normotensive set, we excluded all subjects with hypertension diagnosed (ABP >135/85) and subjects using antihypertensive medication. In the second and unmedicated set, we only excluded the 29 subjects using antihypertensive medication. The third set included all available subjects. To obtain ABP values in these medicated subjects, drug class-specific treatment effect averages, obtained from a recent large systematic review of the effect of antihypertensive treatment on *ambulatory* BP,[6] were added to the observed pressures. Unlike substitution methods, this adjustment makes no assumptions regarding the underlying reasons for treatment and keeps the relative ranking of the treated subjects intact.

Results

On average, 27 (±4) BP measurements (≈13.5 hours) took place during the recording period, of which, on average, 13 (±5) were during sitting posture (≈6.5 hours, which is 48% of the total monitoring period). Although the sample was previously selected based on the presence of at least 2 family members with extreme scores on personality questionnaires, their scores did not correlate significantly with hypertension diagnosis, or with SBP and DBP. Throughout the day, men had significantly higher SBP and DBP than women. At all 3 periods, age was significantly correlated with SBP (0.24 to 0.33) and DBP (0.31 to 0.35). Both sex and age were kept as covariates in all further model-fitting analyses.

Body mass index correlated significantly with both SBP (0.24 to 0.31) and DBP (0.20 to 0.25). Because several studies reported a genetic covariation between BP and body mass index,[4,22,23] and because genetic variance is removed when shared genes influence both variable and covariate, we intentionally did not include body mass index as covariate.

Hypertension

In our sample, 115 (14.5%) of the 792 subjects received a hypertension diagnosis based on their ambulatory recording, with 29 of them receiving antihypertensive medication. Among the hypertensive were 31 MZ twins. The homogeneity of covariances over the sexes and between DZ twins and siblings was confirmed, and no evidence for a difference in twin pair versus singleton sibling pair correlation in hypertensive risk was found. The liability threshold was higher for women compared with men, and higher for younger versus older subjects. The sex- and age-corrected tetrachorical correlations for the liability dimension were 0.62 for MZ twins and 0.29 for DZ twins, indicating genetic influences. This was confirmed by model fitting, the results of which are shown in Table 1. Leaving out both shared environmental and genetic influences from the model (E-model) caused a large increase in χ^2, indicating a significant worsening of the fit. This shows a clear influence of *familial* factors on hypertension. Statistical power was insufficient to discriminate be-

TABLE 2. Means (SD) for Ambulatory SBP and DBP at the 3 Daily Periods

Time of Day	BP (mm Hg)	Sex	Normotensives (645<N<657)	Unmedicated Set of Subjects (747<N<759)	Full Set of Subjects (772<N<786)
Morning	SBP	M	129.8 (9.1)	133.5 (11.4)	134.2 (12.1)
		F	124.2 (8.3)	125.9 (10.1)	126.7 (11.3)
	DBP	M	79.3 (6.4)	82.5 (8.7)	83.2 (9.4)
		F	77.4 (6.5)	80.8 (7.5)	81.3 (8.3)
Afternoon	SBP	M	129.6 (8.1)	132.6 (10.1)	133.2 (10.9)
		F	122.9 (8.5)	125.9 (10.1)	125.3 (10.2)
	DBP	M	77.4 (6.4)	80.4 (8.2)	81.1 (8.9)
		F	77.4 (6.0)	78.6 (7.1)	79.1 (7.7)
Evening	SBP	M	129.0 (8.5)	132.1 (10.4)	132.7 (10.9)
		F	122.9 (8.1)	124.7 (10.1)	125.3 (10.8)
	DBP	M	76.0 (6.3)	79.3 (8.7)	79.9 (9.2)
		F	76.6 (6.8)	77.9 (7.8)	78.4 (8.4)

SD indicates standard deviation; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; M, male; F, female.

tween genetic influences and shared environmental influences, but given the pattern of twin correlations and the values of Akaike's Information Criterion of the AE and CE models, it is most likely that the AE model is the preferred model. In the AE model, variance in hypertension diagnosis is, for 61%, explained by genetic influences.

Ambulatory BP

Table 2 presents the mean ABP for the 3 periods of the day in the normotensive, unmedicated, and full set of subjects. It illustrates the impact of excluding subjects with hypertension and/or using antihypertensive medication. Although the means do not dramatically change (2% to 4.5%), strict exclusion brings about a 30% to 39% reduction in the standard deviation in comparison to the "true" population. Exclusion of medicated subjects led to much smaller changes in means (−0.5% to 0.5%) and moderate reductions in standard deviations (1% to 10.5%). Next, the resemblance between MZ twins and between DZ twins or sibling pairs was examined by calculating age-adjusted Pearson correlations, stratified by sex, as shown in Table 3. Throughout, a larger MZ than DZ correlation is evident, suggesting the presence of additive genetic and unique environmental influences.

Multivariate Genetic Analyses

The means and variances of both SBP and DBP were equal for MZ and DZ twins and for singleton siblings. Importantly, we found no twin–singleton differences in ABP in all 3 sets of subjects, suggesting that results obtained in twins can be generalized to singletons.

Multivariate model-fitting resulted in the preference for a model without shared environmental factors (AE model) over the full model (ACE model) for all 3 sets of subjects. Statistical power was sufficient to discern the AE and CE model, because quantitative analyses have higher statistical power than the ordinal analyses performed for hypertension status. Although there was sufficient power (at $\beta=0.80$, $\alpha=0.05$) to detect effects of 23% or higher, no significant common environmental effect was found. We further tested the hypothesis that a common latent trait was underlying BP

TABLE 3. Resemblance Between MZ and DZ/Sib Pairs for Ambulatory SBP and DBP

		SBP		DBP	
Time of Day	Sex of Pairs	rMZ	rDZ/sib	rMZ	rDZ/sib
Morning	M	**0.72/0.60/0.68**	**0.38/0.38/0.41**	**0.42/0.63/0.68**	**0.21/0.34/0.40**
	F	**0.44/0.56/0.49**	**0.13/0.23/0.27**	**0.34/0.51/0.51**	**0.21/0.28/0.33**
	Opposite sex	—	0.09/0.16/**0.26**	—	0.16/0.12/0.10
Afternoon	M	**0.40/0.62/0.60**	**0.27/0.25/0.32**	**0.63/0.70/0.65**	**0.38/0.39/0.43**
	F	**0.59/0.68/0.64**	**0.18/0.23/0.27**	**0.62/0.72/0.73**	**0.30/0.30/0.35**
	Opposite sex	—	0.08/0.18/**0.26**	—	0.19/0.14/**0.15**
Evening	M	0.34/**0.49/0.59**	**0.35/0.32/0.39**	0.31/**0.49/0.56**	0.17/**0.45/0.43**
	F	0.19/**0.35/0.40**	**0.18/0.19/0.27**	0.21/**0.43/0.45**	**0.18/0.21/0.27**
	Opposite sex	—	0.17/0.11/**0.24**	—	0.18/0.09/**0.15**

Shown are the age-corrected correlations for the normotensive set of subjects/the set excluding medicated subjects/the full set of subjects (with ABP corrected for medication).

Correlations that are significant at a 0.05 level are in bold.

MZ indicates monozygotic; DZ, dizygotic; sib, singleton siblings.

TABLE 4. Heritability Estimates for SBP and DBP Under the Common Pathway Model

		Common Pathway, %		Specific, %
BP	Time of Day	A	E	E
Normotensive set of subjects				
DBP	Morning	40 (28–53)	23 (13–35)	37 (31–44)
	Afternoon	55 (39–70)	30 (19–47)	15 (9–21)
	Evening	31 (20–41)	17 (10–28)	52 (46–59)
SBP	Morning	38 (24–51)	29 (18–44)	32 (27–38)
	Afternoon	50 (32–65)	38 (24–56)	12 (7–18)
	Evening	32 (19–44)	24 (14–38)	44 (38–50)
Unmedicated set of subjects				
DBP	Morning	52 (39–63)	23 (15–36)	24 (20–29)
	Afternoon	61 (46–73)	27 (17–41)	12 (7–14)
	Evening	43 (32–53)	19 (12–30)	37 (32–42)
SBP	Morning	49 (34–62)	30 (18–45)	22 (18–26)
	Afternoon	57 (41–71)	35 (22–51)	9 (6–12)
	Evening	42 (29–54)	26 (16–39)	38 (27–36)
Full set of subjects				
DBP	Morning	55 (43–65)	23 (15–35)	22 (18–26)
	Afternoon	63 (50–74)	27 (17–39)	10 (7–14)
	Evening	46 (35–56)	19 (12–29)	35 (30–39)
SBP	Morning	50 (38–61)	30 (20–42)	20 (17–24)
	Afternoon	57 (44–69)	34 (24–48)	9 (6–12)
	Evening	44 (33–55)	27 (18–38)	29 (25–34)

Shown are the heritability estimates for the normotensive set of subjects, the unmedicated set of subjects, and the full set of subjects.

The 95% confidence intervals are given in parentheses.

at all 3 periods of the day (common pathway model). This model was preferred over the initial independent pathway model in all 3 sets of subjects. We found no specific genetic influences for each of the daily periods, and the largest part of unique environmental influences was also common to all 3 periods. Table 4 shows the common pathway estimates for A, which corresponds to the heritability, and for E, which corresponds to the influence of the common environmental factor. The specific E estimates represent unique environmental influences that are specific to each of the periods of the day.

The highest heritability estimates were found in the full set of subjects. In comparison to the results on the normotensive subjects, heritability estimates were substantially higher (SBP, +7% to 12%; DBP, +8% to 15%). Furthermore, confidence intervals were wider for the normotensive subjects compared with the full set of subjects. An increase in heritability was already seen when unmedicated subjects were included, but only when medicated subjects were included did we find nonoverlapping confidence intervals with the normotensives.

Individual differences in daily physical activity on the measurement day did not confound the genetic analyses of ABP. When these analyses were repeated using BP measurements obtained during sitting activities, the results were essentially unchanged.

Discussion

Based on daytime ambulatory measurements of SBP and DBP, obtained in 792 twins and singleton siblings, the present study showed that the individual differences in hypertension status are, for 61%, genetically determined. Heritability estimates for ambulatory SBP and DBP were between 44% and 63% when no exclusion criteria were upheld. These estimates correspond well to those found in previous ambulatory and laboratory/clinical studies in other large adolescent and adult healthy twin samples.[2,10,12,13] Our study had a number of strengths in design that provide confidence in its outcome. The extended twin design increases the statistical power to distinguish between components of A, C, and E compared with a design including only MZ and DZ twins.[15] Furthermore, it allowed us to test the possibility that results obtained on singleton sibling pairs differed somehow from those obtained in twin pairs. This is important because the lower birth weight in twins might be considered to reflect an impaired fetal environment, which, according to the "Barker hypothesis," may impact on BP regulation.[24] By comparing singletons with twins from the same family, the 2 comparison groups are perfectly matched for familial influences (same parents, same womb, although at a different time, and same family environment). Our analyses showed that MZ and DZ twins and singleton siblings did not differ from each other in means or variances on any of the ABP measures. Importantly, sibling–sibling covariance did not differ from sibling–twin or DZ–twin covariance, which strongly argues against a special twin intrauterine disadvantage with deleterious effects on adult ABP. The absence of any twin–singleton difference repeats previous findings in resting laboratory BP[25] and indicates that estimates of the heritability of ABP from twin studies are not systematically biased and can be generalized to the general population.

Exclusion of hypertensive subjects clearly distorted MZ and DZ twin correlations, as well as the variances. Excluding medicated subjects further increased the distortion, although the effect was only very minor in this population. Our results showed that restricting the sample to normotensives only not only caused a decrease in total variance but also specifically reduced heritability estimates. With this result, we extend the earlier findings of Cui et al[26] on conventional office BP to prolonged BP measurements in naturalistic settings. The effect of excluding groups of subjects, on grounds of hypertension and/or medication, is undesirable because the reduced heritability estimates directly lead to a loss of power in linkage studies. This effect was convincingly illustrated by Hunt et al,[27] who showed that removing medicated subjects from the sample led to the disappearance of a quantitative trait locus for conventional office SBP on chromosome 6.

The substantial heritability of office BP has motivated many large-scale efforts to identify hypertension-predisposing genes through linkage[28] approaches. Because ABP is a better predictor of target organ damage,[7] cardiovascular morbidity, and mortality[8,9] than office BP, these gene finding attempts may be well-served by using ABP. Here, we show that genetic variance of ABP is sufficiently high to justify its use in genome searches. The repeated-measures

structure inherent in ambulatory monitoring brings further advantages. We separated the entire ambulatory recording into 3 daily periods, allowing for the possibility that different genetic factors would affect BP regulation during leisure (evening) and work (morning, afternoon) periods. For both SBP and DBP, a common factor influenced all 3 periods. There were no separate genetic factors influencing BP at different periods of the day. From a gene finding point of view, the common genetic factor structure is advantageous on 2 accounts. The repeated-measures structure increases statistical power to find genes in linkage analysis.[29] Additionally, these genes, by virtue of having a pervasive influence on SBP or DBP across all situations, will also have the largest clinical relevance.

Limitations

An important limitation to our study is the lack of night-time recordings. We opted not to burden our subjects by asking them to continue wearing the BP monitor at night. In our experience, this causes large attrition in nonpatient populations. In family-based studies, the loss of a single subject is more hard-felt than in population samples, in which an additional randomly drawn subject can be easily recruited without loss to the overall study design. It is possible, however, that different genetic factors come into play during the day than at night. Some indication for this possibility, although the confidence intervals of the estimates for the 3 daily periods were overlapping, is seen in the systematically lower heritability in the evening compared with morning and, particularly, afternoon recordings.

Our sample consisted of young white adults aged mainly between 20 and 40, with an age range between 15 and 81 years. Therefore, generalization of our results beyond the main age range or to a population of different ethnicity should be performed only hesitantly. A recent family study performed an age-stratified longitudinal genetic analysis of office BP and found little variation in the genetic architecture over time.[30] This suggests that a common set of genes may be contributing to the observed variation in BP across a wide age range. In our sample, separating the analyses of ABP over multiple age cohorts would have compromised statistical power to detect, for instance, twin–singleton differences.

Perspectives

Genetic contribution to the variance in BP is very likely to be polygenic, with only very small contributions of the individual QTLs to the final hypertensive risk. Future gene-finding studies, particularly linkage studies, should therefore aim to maximize statistical power. In this regard, ABP monitoring has a number of advantages over conventional office measurements. Heritability of ABP is comparable to office BP, but the genes underlying ABP are likely to have better predictive validity for target organ damage,[7] cardiovascular morbidity, and mortality.[8,9] Ambulatory recording has an intrinsic multivariate nature, and the repeated, highly correlated BP measures can be exploited to reduce measurement error and improve the estimation of the latent genetic factor. Our findings further show that a part of the genetic variance in ABP is lost when hypertensive (and/or medicated) subjects are excluded. In future linkage and association studies, such exclusion should be avoided.

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