Acta Genet Med Gemellol 39:99-108 (1990)


Sixth International Congress
on Twin Studies

# Chronological Changes in Genetic Variance and Heritability of Systolic and Diastolic Blood Pressure Among Chinese Twin Neonates

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**Abstract.** In order to examine the chronological changes in genetic variance and heritability of arterial systolic and diastolic blood pressure (SBP and DBP) of Chinese infants in Taiwan, a total of 339 same-sexed twin neonates born in four major general teaching hospitals in Taipei City were studied. Based on placentation and 12 red blood cell antigens, 274 monozygotic (MZ) and 65 dizygotic (DZ) twin pairs were identified and followed up to the age of one year. Both SBP and DBP were measured by Doppler blood pressure monitor. Within-pair mean squares of SBP and DBP were consistently smaller in MZ than DZ twins at ages one month and over. The findings remained unchanged after the adjustment for the effects of age, sex, gestational age, placentation and physical state during blood pressure measurement. Falconer's heritability indices for adjusted SBP and DBP at ages two months and over ranged from 0.29 to 0.55 and from 0.27 to 0.45, respectively. The study indicates an important genetic influence on blood pressure during infancy.

**Key words: Heritability, Blood pressure, Infants, Twins**

## INTRODUCTION

Hypertension has been well documented as a major risk factor of coronary heart diseases [17] and cerebrovascular diseases [30]. It is essential to explore the factors

responsible for the elevation of blood pressure in order to prevent its occurrence.

Based on family and twin studies, many investigators have strongly suggested that there is an important genetic component in the determination of adult blood pressure in spite of the discrepancy in their study population and statistical analyses [2,3,5,6,12,23,24,26]. Similarity of blood pressure in childhood among siblings has also been established [16,32]. As the prevention of hypertension and atherosclerosis in childhood is more effective and efficient than in adulthood [13], the evaluation of the degree in the expression of blood pressure-associated genetic factors and the change in gene-environment interaction at different ages becomes important for the selection of a critical period to control cardiovascular diseases.

The purpose of this report is to present the results of a twin study aimed to assess the chronological changes in genetic variance and heritability of systolic and diastolic blood pressure during infancy.

## MATERIALS AND METHODS

### Twin Sample

From October 1, 1985 to December 31, 1988, all 844 twin neonates born in four major general teaching hospitals in Taipei City were chosen as the study population. The clinical record of each twin was reviewed and abstracted in details. Exclusion criteria included stillbirth and/or congenital malformations affecting one or both cotwins (63 pairs), opposite sex (143 pairs), and undetermined zygosity (116 pairs). During the study period, blood pressure measurement was not carried out in one hospital for some difficulties in the administrative arrangement after September 1987, so that blood pressure data were not available for twins in this hospital thereafter. Totally, 339 same-sexed twin pairs were recruited and followed up to the age of one year.

### Zygosity Determination

Zygosity of twin pairs was determined by placentation and blood typing on 12 red blood cell antigens (A, B, C, c, D, E, e, M, N, $Le^a$, $Le^b$, and $P_1$). Monochorionic pairs as well as pairs concordant in all antigen markers were classified as MZ. Dichorionic pairs and pairs discordant for one or more antigens were diagnosed as DZ. Accordingly, 274 MZ pairs (127 male and 147 female) and 65 DZ pairs (38 male and 27 female) were identified.

### Blood Pressure Examination

Arterial blood pressure was measured by a nurse using a Doppler ultrasound blood

pressure monitor (Critikon Dinamap TM Monitor Model 1846) according to a standard protocol. The physical state of the twin subjects (asleep, awake and quiet, awake and active) during blood pressure measurement was also recorded. Three readings were made and their mean value was used in the data analysis. Blood pressures of 339 neonates were measured from birth to 7 days of life in the baby rooms of the study hospitals. Follow-up home visits were scheduled at the age of one month (30 ± 7 days), two months (60 ± 7 days), six months (180 ± 14 days), and twelve months (365 ± 14 days). Follow-up blood pressure measurements were available for 102, 104, 159 and 124 twin pairs at 1, 2, 6 and 12 months of age, respectively.

### Data Analysis

The methods used in this study were based on the analysis of variance described by Christian et al [7,8]. A $t'$ test was used first to assess the difference in means between MZ and DZ twins.

The within- and among-pair mean squares (MSW and MSA) were calculated to derive intrapair correlation coefficients (r) for MZ and DZ twins, respectively. A two-tailed $F'$ test [14] was used to examine the equality of the total variance in MZ and DZ twins. If there was no evidence of unequal total variance, the within-pair genetic variance [19] and Falconer's heritability index ($h^2$) [11] were calculated. On the other hand, if the total variance was significantly different between MZ and DZ twins, the among-component genetic variance [11] and Christian's heritability index [8,9] were used instead.

The F ratio comparing MSA with MSW of DZ twins [8] was further employed to test the assumption of equal environmental covariance in MZ and DZ twins. If this ratio is not significantly greater than 1.0, greater environmental covariance for MZ than DZ twins should be suspected. To adjust for possible effects of age, sex, gestational age, placentation, physical state during blood pressure measurement, height, and weight, a multiple linear regression model with blood pressure as dependent variable and these confounders as independent variables was derived. As height and weight was not significantly associated with both systolic and diastolic blood pressure (SBP and DBP) during infancy, they were not included in the regression equation. The individual residual values derived from the observed values and predicted values based on the regression equation were then computed and used as the data input for analysis.

## RESULTS

### Means of Blood Pressure

Means and standard deviations of SBP and DBP in MZ and DZ twins are shown in Table 1. The mean values of SBP and DBP were observed to increase with age

for both MZ and DZ twins. In general, DZ twins had a slightly higher SBP and DBP than MZ twins, but the difference was not significant except for the DBP at six months of age.

**Table 1 - Means and standard deviations of systolic and diastolic blood pressure in MZ and DZ twins from birth to one year of age**

| Age | Blood pressure | MZ pairs | | | DZ pairs | | | t′ |
|---|---|---|---|---|---|---|---|---|
| | | N | Mean | (SD) | N | Mean | (SD) | |
| Newborn | SBP | 274 | 58.1 | (7.4) | 65 | 59.2 | (7.2) | −1.25 |
| | DBP | 274 | 37.6 | (5.5) | 65 | 37.9 | (5.4) | −0.52 |
| One month | SBP | 81 | 71.2 | (10.4) | 21 | 73.5 | (11.4) | −0.92 |
| | DBP | 81 | 41.0 | (7.2) | 21 | 40.4 | (8.0) | 0.30 |
| Two months | SBP | 82 | 82.5 | (9.5) | 22 | 81.5 | (13.6) | 0.47 |
| | DBP | 82 | 46.0 | (9.3) | 21 | 44.4 | (11.5) | 0.86 |
| Six months | SBP | 124 | 92.9 | (9.2) | 34 | 94.5 | (8.1) | −1.08 |
| | DBP | 124 | 51.3 | (9.8) | 35 | 54.9 | (8.3) | −2.52* |
| One year | SBP | 87 | 95.1 | (8.0) | 35 | 96.4 | (7.7) | −0.95 |
| | DBP | 88 | 52.4 | (8.5) | 36 | 54.2 | (7.3) | −1.50 |

* $P < 0.05$.

## Crude MSAs, MSWs and Equality of Total Variance

The MSW and MSA of SBP and DBP at different ages for MZ and DZ twins are shown in Table 2. Generally speaking, MSWs were lower in MZ than in DZ twins. There was no significant difference in total variance between MZ and DZ

**Table 2 - Within-pair mean squares (MSW) and among-pair mean squares (MSA) of systolic and diastolic blood pressure by zygosity from birth to one year of age**

| Age | Blood pressure | MZ pairs | | DZ pairs | | F′ test for total variance | F test for $MSA_{DZ}/MSW_{DZ}$ |
|---|---|---|---|---|---|---|---|
| | | MSW | MSA | MSW | MSA | | |
| Newborn | SBP | 25.5 | 87.0 | 27.0 | 80.9 | 1.04 | 3.00** |
| | DBP | 16.3 | 46.8 | 14.5 | 44.5 | 1.07 | 3.07** |
| One month | SBP | 27.9 | 185.2 | 43.6 | 238.2 | 1.32 | 5.46** |
| | DBP | 21.6 | 81.0 | 39.3 | 136.0 | 1.71* | 3.46** |
| Two months | SBP | 41.2 | 116.9 | 63.0 | 156.0 | 1.39 | 2.48* |
| | DBP | 39.1 | 146.8 | 45.8 | 108.0 | 1.21 | 2.36 |
| Six months | SBP | 31.4 | 137.5 | 47.9 | 104.5 | 1.11 | 2.18* |
| | DBP | 41.0 | 137.6 | 58.2 | 109.3 | 1.06 | 1.88* |
| One year | SBP | 29.0 | 94.7 | 37.6 | 77.8 | 1.07 | 2.07* |
| | DBP | 39.6 | 107.9 | 48.1 | 58.1 | 1.39+ | 1.21 |

+ $P < 0.2$; * $P < 0.05$; ** $P < 0.01$.

https://doi.org/10.1017/S0001566000005614 Published online by Cambridge University Press

**Table 3 - Multiple linear regression of blood pressure on the age, sex, gestational age, placentation and physical state during blood pressure measurement**

| Variable[a] | Newborn | | One month | | Two months | | Six months | | One year | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SBP | DBP | SBP | DBP | SBP | DBP | SBP | DBP | SBP | DBP |
| Age (days) | 1.03** | 0.71** | 0.36** | 0.02 | −0.01 | 0.08 | −0.01 | −0.09 | −0.01 | −0.00 |
| Sex | −0.22 | 0.64 | 3.20+ | 0.96 | −1.58 | 2.26 | 2.98* | 2.34+ | 1.31 | 1.17 |
| Gestational age | 0.85** | 0.61** | 1.22** | 0.58** | 0.48 | 0.43 | 0.63* | 0.35 | 0.06 | −0.27 |
| Physical state: | | | | | | | | | | |
| Awake and quiet | — | — | 4.00* | 5.17** | * 3.79* | 8.28** | 5.66** | 6.73** | 1.17 | 7.53** |
| Awake and active | — | — | — | — | 9.94** | 10.34** | 6.31** | 7.88** | 3.64 | 6.27* |
| Placentation: | | | | | | | | | | |
| Monoplacental dichorionic | 0.04 | 0.45 | — | — | — | — | — | — | — | — |
| Monochorionic | 0.61 | 0.28 | — | — | — | — | — | — | — | — |

[a] Sex, physical state and placentation were input as dummy variables. The reference group of sex, physical state and placentation was defined as female, asleep state, and separate placenta, respectively.

+ $P < 0.2$; * $P < 0.05$; ** $P < 0.01$.

twins for SBP and DBP in most age groups. As the total variance in MZ and DZ twins was significantly different for the DBP at the age of one month and of twelve months, among-component genetic variance and Christian's heritability index were considered as appropriate measures for genetic variance and heritability.

All MSWs of DZ twins were significantly less than MSAs except for DBP at one year of age. This indicated a similar environmental covariance in MZ than DZ twins.

## Multiple Regression Analysis of SBP and DBP

Regression coefficients of age, sex, gestational age, physical state and placentation in the multiple regression analysis of blood pressure are shown in Table 3. Age in days was positively associated with both SBP and DBP in newborn period and with SBP at one month of age.

Significantly positive associations with gestational age were found for both SBP and DBP in the newborn period and at the age of one month. Although gestational age was also associated with SBP at six months, a stronger influence was observed before the age of two months.

Sex was significantly associated with SBP at the age of six months. Physical state was significantly associated with blood pressure at the age of one month and thereafter.

**Table 4 - Adjusted within-pair mean squares (MSW) and among-pair mean squares (MSA) of systolic and diastolic blood pressure by zygosity from birth to one year of age**

| Age | Blood pressure | MZ pairs | | DZ pairs | | F′ test for total variance | F test for $MSA_{DZ}/MSW_{DZ}$ |
|---|---|---|---|---|---|---|---|
| | | MSW | MSA | MSW | MSA | | |
| Newborn | SBP | 24.7 | 78.3 | 26.0 | 61.4 | 1.18 | 2.36** |
| | DBP | 16.1 | 42.6 | 13.1 | 37.9 | 1.15 | 2.90** |
| One month | SBP | 27.5 | 142.7 | 41.8 | 154.3 | 1.15 | 3.69** |
| | DBP | 15.5 | 68.3 | 32.2 | 99.6 | 1.57* | 3.09** |
| Two months | SBP | 35.4 | 107.9 | 73.3 | 156.6 | 1.60* | 2.14* |
| | DBP | 42.1 | 113.7 | 60.7 | 97.5 | 1.01 | 1.61 |
| Six months | SBP | 33.4 | 137.4 | 41.5 | 83.3 | 1.37+ | 2.01* |
| | DBP | 42.8 | 135.9 | 62.6 | 141.6 | 1.14 | 2.26* |
| One year | SBP | 29.4 | 97.2 | 38.1 | 81.5 | 1.06 | 2.14* |
| | DBP | 46.6 | 108.2 | 53.9 | 80.2 | 1.15 | 1.49 |

+ $P < 0.2$; * $P < 0.05$; ** $P < 0.01$.

https://doi.org/10.1017/S0001566000005614 Published online by Cambridge University Press

## Adjusted MSAs and MSWs

The MSW and MSA for adjusted SBP and DBP in MZ and DZ twins are shown in Table 4. After adjusting for age, sex, gestational age, placentation and physical state during blood pressure measurement, all MSWs of MZ twins remained smaller than those of DZ twins at ages of one month and over. There was no significant difference in total variance between MZ and DZ twins except for the DBP at one month and the SBP at two and six months. Adjusted MSWs of DZ twins were still significantly less than adjusted MSAs in most age groups except for the DBP at ages of two and twelve months .

**Table 5 - Unadjusted and adjusted intrapair correlation coefficients and heritability estimates of blood pressure from birth to one year**

| Age | Blood pressure | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|---|
| | | $r_{MZ}$ | $r_{DZ}$ | $h^2$ | $r_{MZ}$ | $r_{DZ}$ | $h^2$ |
| Newborn | SBP | 0.55 | 0.50 | 0.09 | 0.52 | 0.41 | 0.23 |
| | DBP | 0.48 | 0.51 | — | 0.45 | 0.49 | — |
| One month | SBP | 0.74 | 0.69 | 0.10 | 0.68 | 0.57 | 0.21 |
| | DBP | 0.58 | 0.55 | 0.05[a] | 0.63 | 0.51 | 0.24[a] |
| Two months | SBP | 0.48 | 0.42 | 0.11 | 0.51 | 0.36 | 0.29[a] |
| | DBP | 0.58 | 0.40 | 0.35 | 0.46 | 0.23 | 0.45 |
| Six months | SBP | 0.63 | 0.37 | 0.52 | 0.61 | 0.33 | 0.55[a] |
| | DBP | 0.54 | 0.31 | 0.47 | 0.52 | 0.39 | 0.27 |
| One year | SBP | 0.53 | 0.35 | 0.37 | 0.54 | 0.36 | 0.35 |
| | DBP | 0.46 | 0.09 | 0.74[a] | 0.40 | 0.20 | 0.40 |

— = Falconer's heritability index less than zero.

[a] Christian's heritability index was less than zero for the crude and adjusted DBP at one month, and the adjusted SBP at two months. The index for the crude DBP at one year and the adjusted SBP at six months was 0.92 and 0.84 respectively.

## Unadjusted and Adjusted Heritability of Blood Pressure

Unadjusted and adjusted age-specific intrapair correlations and estimates of heritability are shown in Table 5. All intrapair correlations were higher in MZ than DZ twins except for the DBP in the newborn period. For SBP, the $h^2$ before adjustment increased gradually from 0.09 in the newborn period to 0.52 at six months of age, and decreased to 0.37 at one year. At most ages, the adjustment for age, sex, gestational age, physical state and placentation produced an increase in $h^2$, but the pattern of chronological change remained the same. Falconer's heritability indices of DBP ranged from 0.35 to 0.74 for unadjusted DBP and from 0.27 to 0.45 for adjusted DBP after the age of two months. The indices ranged from 0.11 to 0.52 for unadjusted SBP and from 0.29 to 0.55 for adjusted SBP after the age of two months. Although heritability of unadjusted DBP increased steadily from the age

of two months to the age of one year, there was no consistent increasing pattern in adjusted DBP during the same age interval.

## DISCUSSION

The variability of blood pressure among different populations and/or individuals cannot readily be explained by the diversity of life style only [21]. Genetic predisposition has long been assumed to account for a part of the unexplained variation. In the past decades, numerous studies were conducted to explore the relative contributions of hereditary and environmental components in the determination of blood pressure. A significant genetic influence on blood pressure has been well documented. In this study, MSWs of SBP and DBP were consistently smaller in MZ than DZ twins after the age of one month, although genetic variance for both SBP and DBP was not statistically significant. A sizable heritability was also observed during infancy, especially after the age of two months. The Falconer's heritability indices, adjusting for age, sex, gestational age, and physical state at ages of two months or over, ranged from 0.29 to 0.55 for SBP and from 0.27 to 0.45 for DBP. These findings are consistent with those of previous studies to a certain degree [1,6,15,20,25,29]. However, there were some differences in the estimated heritability in these studies. This may be due to different age distributions, biological makeup, environmental factors and lifestyles, as well as to study designs and data analysis.

Many factors associated with growth and development are related to the change of blood pressure in infancy. Age, height, weight, and sexual maturity have been considered to account for a sizable variation of blood pressure in children and adolescents [18,28]. The association between body size and blood pressure in infancy has seldom been reported. Body size was not associated with blood pressure in our study either. However, gestational age and physical state were strongly associated with blood pressure in this study.

A major issue in the estimation of genetic variance and heritability in twin studies is the assumption of the equality of environmental correlations in MZ and DZ twins. If the environmental correlation of MZ twins is greater than that of DZ twins, the heritability is overestimated. It has been reported that chorionic type has an effect on the within-pair variability of birth weight [4] and cord blood cholesterol levels [10]. As all DZ twins and only about 30% of MZ twins are dichorionic, the intrauterine competition and distribution of essential nutrients might be different between MZ and DZ twins. If the intrauterine environment has an effect on newborn blood pressure, it may affect not only the within-pair variance, but also the among-pair variance. Therefore, placentation was also considered to improve the estimation of among-pair variance in this study. However, the within-pair variance still remained unchanged through this adjustment. In other words, the effect of placentation on within-pair variance should still be taken into consideration when heritability is estimated. As no substantial difference in within-pair variance between MZ and DZ twins was observed, the possibility of an overestimation in heritability is rather small in this study. Actually, if a monochorionic placenta

increases the within-pair variance in MZ twins, heritability will be underestimated.

Numerous studies attempted to evaluate the multifactorial etiology of blood pressure. However, the chronological pattern of heritability in blood pressure has not, to our knowledge, been documented. In the present study, it is interesting to observe an increasing trend in heritability for SBP from the newborn period to the age of six months and an important genetic component in DBP after two months of age. Although there is no well-established mechanism to explain these findings in humans, results from animal experimentation suggest genetic determination of a variety of physiological factors associated with the regulation of arterial blood pressure from the fetal period to maturity, ie, vascular structures, vascular reactivity, and neurohormonal system [22,31]. On the other hand, blood pressure increased markedly during the first two months of life and only slightly thereafter. This is not readily explained by the rapid changes in anthropometric characteristics, and sequential genes associated with blood pressure control and acting only during early life might also be involved. In addition, a previous study on spontaneously hypertensive rat suggested a significant interaction between genotype and salt intake on blood pressure [27]. The changes of certain environmental factors may modify the expression of various genes at different ages. This may also explain the chronological changes in heritability of SBP and DBP in this study.

**Acknowledgments.** This study was supported by grants from National Science Council, Republic of China (NSC-75-0412-B002-23, NSC-76-0412-B002-42, NSC-77-0412-B002-18, NSC-78-0412-B002-117).

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