Heritability of Venous Function in Humans

Marina Brinsuk, Jens Tank, Friedrich C. Luft, Andreas Busjahn, Jens Jordan

Objectives—Venous function contributes to the pathogenesis of thrombophlebitis, venous thrombosis, and possibly to arterial hypertension. Venous disease is presumably heritable; however, the genetic variance of venous function is unknown.

Methods and Results—We determined the heritability of venous function in 46 twin pairs (24 monozygotic, age 35±11 years, 14 men, 34 women; 22 dizygotic, age 30±8 years, 19 men, 25 women). After a resting phase in the supine position, we determined venous function in both legs by impedance plethysmography. Venous capacity was determined by a standardized protocol. In addition, we obtained venous pressure volume curves by slowly deflating a thigh cuff from 60 to 0 mm Hg. Venous compliance was determined as the steepest part of the venous pressure volume curve. Heritability was estimated using a path modeling approach. Unadjusted heritability was 0.6 (P<0.05) for venous capacity and 0.9 (P<0.05) for venous compliance. The heritability estimate for venous capacity decreased to 0.3 after adjustment for age, body mass index, and body fat. The heritability estimate for venous compliance remained essentially unchanged after adjustment for sex and age.

Conclusions—We conclude that venous function is strongly influenced by genetic factors. The genes involved may influence venous disease states. (Arterioscler Thromb Vasc Biol. 2004;24:207-211.)

Key Words: twin study ■ genetics ■ plethysmography ■ venous compliance

A pproximately 75% of the circulating blood volume is contained in veins. Therefore, relatively small changes in venous function may have a substantial effect on the cardiovascular system. For example, an increase in venous tone may cause a shift of blood volume from the periphery toward the heart and increase cardiac output. This mechanism may contribute to increased cardiac output in the earlier stages of essential hypertension. Venous function becomes particularly important during assumption of upright posture as 500 to 1000 mL are pooled below the diaphragm. Variability in the amount of blood that is pooled during standing influences the propensity to experience orthostatic symptoms. Venous function may also contribute to the pathogenesis of varicose veins, thrombophlebitis, and venous thrombosis. Thus, genes that influence venous function might play an important role in a variety of common cardiovascular ailments. Indeed, ≈60% of the variation in the susceptibility to venous thrombosis is related to genetic factors. A positive family history substantially increases the likelihood to suffer from varicose veins, vasovagal syncope, or essential hypertension. However, the research on the genetics of all these conditions has largely neglected the possibility that venous function may be an important intermediate phenotype. The responsiveness of veins to adrenergic stimulation is influenced by genetic factors. Yet, the mechanical properties of veins, such as compliance and capacity, may be more relevant to physiological function. The magnitude of the genetic contribution to these measures is not known. We determined the heritability of venous function in a cohort of normal twins.

Methods

Subjects
We investigated the heritability of venous function in 46 twin pairs. Twenty-four twin pairs were monozygotic (MZ, age 35±11 years, 14 men, 34 women) and 22 twin pairs were dizygotic (DZ, age 30±8 years, 19 men, 25 women). The twin pairs were recruited from the Berlin Twin Register. The subjects underwent a medical history interview and physical examination before the study. Only healthy persons were included in the study. Persons ingesting medications except birth control pills were excluded from the study. Zygosity was determined using 5 microsatellite markers co-amplified by polymerase chain reaction. The probability of a DZ twin pair to share all marker alleles by chance is 0.006. The overall rate of correct classification is >99%. Written informed consent was obtained before study entry as required by the institutional review board.

Study Protocol
Subjects were evaluated at the Franz Volhard Clinical Research Center after an overnight fast. The level of physical activity was assessed with a questionnaire. Height and weight measurements were taken. Skinfold thickness was measured with a caliper (triceps, chest, abdomen, thigh, calf) to estimate body fat content. In addition, we assessed body composition with body impedance analysis (Quadscan 4000, Bodysstat Ltd, Isle of Man, Great Britain). Relative body
pressure. Cuff pressure was plotted against leg volume using data obtained with 10 to 60 mm Hg occlusion pressure. The correlation between cuff pressure and intravenous pressure is lost at lower cuff pressures. Figure 1 shows venous pressure-volume curves in an MZ twin pair. Venous compliance was determined as the steepest part of the venous pressure volume curve using linear regression analysis. We compared the effect of venous occlusion time on venous compliance in seven subjects. Venous compliance was 0.05 ± 0.01, 0.05 ± 0.01, and 0.06 ± 0.02%/mm Hg after 2, 4, and 8 minutes venous occlusion, respectively.

Statistics and Quantitative Genetics
Statistical analysis was conducted using the SPSS program (SPSS Inc., Chicago, IL). All data are expressed as mean ± 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 using the MX program developed by Neale. The variability of any given phenotype within a population can be decomposed into genetic influences (\( \text{Var}_{\text{addGen}} \)), environmental influences shared by the twins within a family (\( \text{Var}_{\text{sharedEnv}} \)), and effects of random environment (\( \text{Var}_{\text{env}} \)).

\[
\begin{align*}
\text{Var} &= \text{Var}_{\text{addGen}} + \text{Var}_{\text{sharedEnv}} + \text{Var}_{\text{env}}. \\
\text{Cov}_{\text{MZ}} &= \text{Var}_{\text{addGen}} + \text{Var}_{\text{sharedEnv}} \\
\text{Cov}_{\text{DZ}} &= 0.5 \text{Var}_{\text{addGen}} + \text{Var}_{\text{sharedEnv}}
\end{align*}
\]

Heritability analysis in twin studies can estimate additive components of genetic variability as well as two environmental influences, shared and nonshared environmental influences. These values estimate the relative amount of the variable’s influence on interindividual differences up to a sum of one. Genetic as well as environmental effects were estimated by the best fitting model as selected by the \( \chi^2 \) value. Adjustments for age, body mass index (BMI), and blood pressure were done by multiple linear regression using unstandardized residuals. In case of significant deviations from normal distribution, the appropriate transformations were applied. To test relations between measures of venous function and potential covariates, correlations were calculated for the total sample as well as for males and females separately. As many covariates were not independent of one another, stepwise multiple regression analysis was applied to determine a minimum set of predictor variables. The setting for a stepwise exclusion of variables was placed at a probability value of >0.5.

Results
MZ and DZ twins had similar age, body mass index, resting blood pressure, and resting heart rate (Table 1). DZ twins were more commonly male, a difference reflected in their values for body fat and lean body mass. Venous function was

<table>
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<th>TABLE 1. Baseline Characteristics, Intra-Class Correlation Coefficients, and Heritability</th>
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<td>Male/female</td>
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<td>Age, y</td>
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<td>Body mass index, kg/m²</td>
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<td>Lean body mass, kg/%</td>
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<td>Venous capacity, %</td>
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<td>Venous compliance, %/mm Hg</td>
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MZ indicates monozygotic twins; DZ, dizygotic twins; \( h^2 \), heritability; and \( r \), intra-class correlation coefficients. *\( p < 0.05 \)
Twin studies have been extensively used to characterize the interaction of genetic and environmental factors on cardiovascular disease and venous function. Venous compliance and venous capacity were highly correlated in MZ twins (Figures 2 and 3). The correlation was much weaker or even absent in DZ twins. For venous compliance, the correlation was 0.60 for venous capacity and 0.90 for venous compliance.

To test whether or not this genetic influence was secondary to genetic influences on body composition, we adjusted our measures of venous function. For venous capacity, the linear regression included age, BMI, and the weight of body fat as significant predictors. The heritability was reduced to 0.3. For venous compliance, the regression included age, sex, BMI, and absolute and relative weight of body fat. The heritability after adjustment was 0.89 and thereby remained virtually unchanged.

**Discussion**

Twin studies have been extensively used to characterize the interaction of genetic and environmental factors on cardiovascular function. Venous compliance and venous capacity were highly correlated in MZ twins (Figures 2 and 3). The correlation was much weaker or even absent in DZ twins. For venous compliance, the correlation was 0.60 for venous capacity and 0.90 for venous compliance.

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**Figure 2.** Correlation in venous compliance between siblings in monozygotic and dizygotic twins. The correlation was much stronger in monozygotic twins compared with dizygotic twins.

**Figure 3.** Correlation in venous capacitance between siblings in monozygotic and dizygotic twins. The correlation was much stronger in monozygotic twins compared with dizygotic twins.
mediated in part by genes that modulate body composition. Because we did not obtain a measure for microvascular filtration or interstitial fluid content in the leg, we were not able to assess a potential genetic link between these measures and venous function.

The genetic effect on venous function might also be important to the pathogenesis of cardiovascular disorders, such as arterial hypertension, chronic venous disease, and orthostatic intolerance. Indeed, the rather high heritability estimates in our study suggest that venous function may be an important intermediated phenotype. Reduced venous compliance has been described in patients with essential hypertension, a disorder that is highly heritable. Therefore, the genes that influence venous compliance may also be relevant for the pathogenesis of arterial hypertension. We present functional data. However, we speculate that subsequent varicosities may be the result of functional attributes that are largely inherited. Indeed, chronic venous disease is strongly influenced by genetic variance. This issue was also addressed in an elaborate genetic analysis of 68 large pedigrees that included 80 nuclear families. The authors found an astoundingly strong genetic variance, namely penetrance frequencies between 70% and 92%. Finally, abnormalities in venous compliance have been described in patients with orthostatic intolerance.

Our study necessarily has some limitations. One potential weakness is that we characterized genetic influences on venous function in a cohort of healthy subjects. Nevertheless, venous disease is common and will likely occur in many of our subjects as they grow older. The genes involved may be extremely difficult to find. However, genes involved in Mendelian diseases were shown to act as quantitative trait loci in the general population, supporting the close relationship between physiological and pathological processes.

Another potential limitation is the methodology and protocol we employed to assess leg volume. Two methods are widely available to determine leg volume changes, namely impedance plethysmography, as in our study, or strain gauge plethysmography. The correlation between the two methods was found to be good in an earlier study. The cuff inflation duration and the leg position, as well as the cuff pressure profile, may have confounded venous function and may have caused a systematic deviation from the “true” venous compliance and capacity. We also cannot exclude the possibility that venous filling was incomplete during our measurements, which may have caused us to underestimate the venous capacity. Another potential limitation is the fact that we used cuff pressure as a surrogate parameter for intravascular pressure to determine venous pressure-volume curves. The relationship between cuff pressure and intravascular pressure may be altered in individuals with increased resting venous pressure. Finally, we cannot exclude the possibility that increased microvascular filtration during occlusion cuff inflation may have led to secondary changes in venous function measurements. Indeed, the applied cuff pressures were certainly above isovolumetric venous pressure. However, we did not see a major difference in the compliance measurements after 2, 4, and 8 minutes of venous occlusion. The strong heritability estimates suggest that even if our data deviated systematically from “true” venous function, they were nevertheless highly reproducible.

Despite these issues, we suggest that venous capacity and compliance are inherited and that both linkage and association studies are suitable to pursue specifically which gene loci and genes are involved. Elucidation of the genes that influence venous function may provide important new insight in the pathophysiology of cardiovascular disorders that are associated with disordered venous function.

Acknowledgments

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References


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