

Heritability of Central Systolic Pressure Augmentation A Twin Study

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Abstract—Less than 50% of the variance in left ventricular mass is explained by conventional factors such as age, blood pressure, and body size. Genetic influences may account for part of the unexplained variance. The central (aortic) pressure augmentation index has been suggested as a noninvasive measure of pulsatile load, which is a likely determinant of left ventricular mass. We quantified the genetic influence on augmentation index and determined the extent to which this influence is dependent on the effects of age, height, heart rate, and blood pressure. We performed a classical twin study composed of 225 monozygotic and 594 dizygotic female white twin pairs aged 18 to 73 years. Augmentation index and mean arterial pressure were based on the central pressure wave derived from the radial waveform as measured by applanation tonometry. Quantitative genetic modeling techniques were used to analyze the data. The heritability of augmentation index was 37%, whereas heritabilities for blood pressure traits varied between 13% and 25%. Most of the variance in augmentation index could be explained by genetic and environmental factors specifically influencing augmentation index. Only a relatively small part of the total variance in augmentation index could be attributed to genes in common with height (3.1%), heart rate (4.6%), and mean arterial pressure (5.6%). Age explained 19% of the total variation in augmentation index. In conclusion, augmentation index has a significant heritable component, which is largely independent of the influence of blood pressure, heart rate, height, and age. Finding genes for the augmentation index could help to unravel pathophysiological mechanisms causing left ventricular hypertrophy and lead to improvements in prevention, diagnosis, and treatment of at-risk populations. (*Hypertension*. 1999;34:●●●-●●●.)

Key Words: genetics ■ twins ■ augmentation index ■ blood pressure ■ aging ■ hypertrophy

Despite large, prospective, epidemiological studies examining determinants of left ventricular mass,¹⁻⁴ <50% of the variance in left ventricular mass is explained by conventional factors such as age, blood pressure (BP), and body size.⁴ It has been suggested that inheritance may account for part of the unexplained variance.⁵⁻⁷ One hemodynamic factor that has been suggested to influence left ventricular mass is pulsatile vascular load,⁸⁻¹⁰ although this has been difficult to measure in large populations. Murgo et al¹¹ showed that patterns of augmentation index (AI) relate to invasively measured pulsatile vascular load. Recent studies indicate that the AI can be measured accurately noninvasively, providing a reliable method of studying arterial properties in a large population.¹²

AI is defined as the ratio of augmented systolic pressure (due to the late systolic peak in the central pressure waveform) to pulse pressure⁸ and represents a measure of a combination of factors related to large arterial function. It is increased in association with arterial stiffness, caused by the degeneration of the arterial wall as a result of repetitive cyclic stress, which is a major determinant of increasing systolic

pressure with age and in patients with hypertension.¹³ Stiffening of the main central arteries also leads to increased velocity of the pulse wave as it travels down the arteries, which causes wave reflections from peripheral sites to return earlier, increasing the dominance of the late systolic peak in the aortic pressure wave. This elevated central systolic pressure increases left ventricular load and myocardial oxygen demand, serves as a stimulus to hypertrophy, and hinders left ventricular ejection, predisposing to left ventricular failure.¹⁴ A second major influence on the AI is the intensity of wave reflection. This may explain the more prominent secondary (augmented) pressure peak in shorter subjects and in women compared with men.¹⁵ By increasing arterial stiffness, age also increases the intensity of wave reflection as a result of a decrease in the attenuation of reflected waves by the relatively stiffer arterial tree. The importance of AI is supported by studies that show this measure to be an independent determinant of left ventricular mass,^{9,16} which is considered a stronger predictor of cardiovascular events than BP.¹⁷

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To date very little is known about the importance of genetic factors in the development of large arterial function. While both systolic (SBP) and diastolic BP (DBP) have been shown to be heritable to a variable extent,¹⁸⁻²² there is no similar information on arterial function itself. Applanation tonometry provides a means whereby information on arterial function, quantified by the AI, can be widely and accurately collected. A feature of AI, however, is its strong dependence on age,^{8,23} height,^{15,16,24} heart rate,^{15,25} and BP.^{15,26} It is therefore possible that any genetic influence on AI is, at least partly, due to genes in common with mean arterial pressure (MAP), heart rate, and height.

The aim of this study, therefore, was to quantify the genetic and environmental sources of individual differences in AI and to determine the extent to which they are mediated by or dependent on the effects of age, height, heart rate, and MAP. A classical twin design was used to answer these questions. AI and MAP were based on the central aortic pressure wave derived from the radial waveform as measured by applanation tonometry^{8,27} in a large sample of unselected female twins across a broad age range. Both univariate and multivariate quantitative genetic modeling techniques were used to analyze the data.

Methods

Subjects

The study cohort was composed of 819 female white twin pairs (225 monozygotic [MZ] and 594 dizygotic [DZ]) aged 18 to 73 years from the St Thomas' UK Adult Twin Registry.²⁸ Twins from the registry were ascertained from the general population through national media campaigns in the United Kingdom.²⁹ Participating twins were unaware of the specific hypotheses tested, and informed consent was obtained from all subjects. The study was approved by the St Thomas' Hospital Research Ethics Committee. Zygosity was determined by standardized questionnaire, and DNA fingerprinting was used for confirmation.²⁹ Information on medical history, medication use, lifestyle, and demographic variables was obtained by standardized nurse-administered questionnaire.

Measures

Subjects were interviewed and studied by trained research nurses. Height was measured to the nearest 0.5 cm with the use of a wall-mounted stadiometer. Weight (light clothing only) was measured to the nearest 0.1 kg with digital scales. Brachial BP was measured with an automated cuff sphygmomanometer (OMRON HEM713C) with the subject in the seated position under standardized conditions. The average of 2 BP readings was recorded.

The radial arterial pressure waveform was recorded with the subject supine with the use of applanation tonometry³⁰ and commercially available acquisition and analysis software (SphygmoCor, PWV Medical). Applanation tonometry records fluctuations in the pressure wave by a high-fidelity transducer incorporated into the tip of a pencil-shaped probe. Radial artery recordings were taken because this artery is ideal for tonometry since the artery is supported by the bone of the radius behind, allowing accurate applanation (flattening) by the probe. From this recording, the central arterial pressure was derived with the use of a generalized transfer function, which has previously been shown to (1) give an accurate estimate of the central arterial pressure waveform and its characteristics,³¹ (2) be constant across individuals, and (3) be constant across conditions as diverse as exercise-related systolic hypertension and the hypotension associated with cardiac failure.^{32,33}

The radial pressure waveform was calibrated to the measured brachial sphygmomanometric pressure, and MAP was derived by integration. The central DBP and MAP were set as equal to the

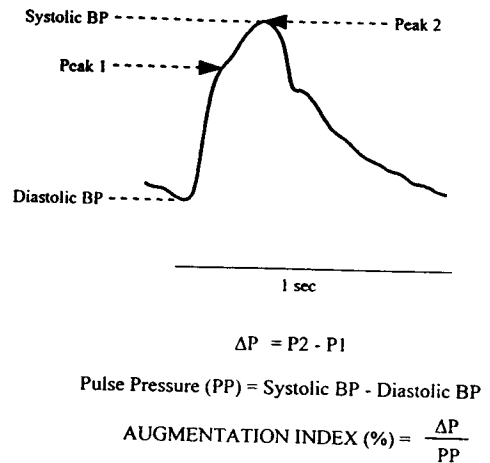


Figure 1. Graphic representation of AI, defined as the ratio of augmented systolic pressure (ΔP) to pulse pressure (PP).

brachial DBP and MAP in the generalized transfer function since it has been shown that these change little in transit down the circulation.^{34,35}

The AI was based on the central aortic pressure wave derived from the radial waveform, as discussed above. As outlined previously, the central pressure waveform is characterized by an early and a late systolic peak in the majority of individuals. The AI is defined as the difference between the early and late pressure peaks divided by the pulse pressure (Figure 1).^{8,11} In our study, intraobserver and interobserver reproducibility for AI, expressed as mean intraclass correlations, were 0.82 and 0.84, respectively.

Analytical Approach

The aims of our analyses were 2-fold. First, to estimate the influence of genetic factors on AI and a range of BP-related variables, we applied univariate model-fitting techniques. Second, to determine the extent to which the genetic influence on AI is dependent on age, height, and MAP, we used multivariate modeling.

Univariate Twin Analysis

Details of univariate model fitting to twin data have been described elsewhere.³⁶⁻³⁸ In short, the technique is based on the comparison of the variance-covariance matrices in MZ and DZ twin pairs and allows separation of the observed phenotypic variance into additive (A) or dominant (D) genetic components and shared (C) or unique (E) environmental components. The latter also contains measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, for example, heritability (h^2), which can be defined as the ratio of additive genetic variance to total phenotypic variance. By incorporating age into the model, the influence of age on the phenotype can also be quantified.³⁹ Extension of this univariate (1 variable) model to a model including multiple variables (multivariate) additionally allows exploration of whether the origin of the covariance between height, heart rate, MAP, and AI is genetically and/or environmentally determined.

Multivariate Twin Analysis

A triangular or Cholesky decomposition^{36,40} including height, MAP, AI, and age was used in the multivariate model fitting. This model enabled us to quantify which part of the (genetic or environmental) variance components was specific to AI and which part was due to the influence of height, heart rate, MAP, or age.

Figure 2 shows the triangular decomposition of the genetic and environmental factors for the 3 phenotypes (and age) included in the analysis. The number of latent factors equals the number of variables. Only 1 twin of a pair is shown. The first factor contributes to all 4 variables, the second factor influences the subsequent 3 variables, and so on. The last factor only influences AI. The observed

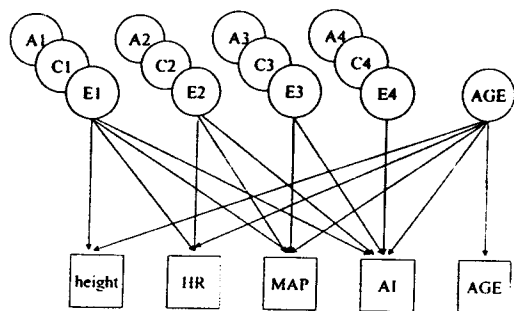


Figure 2. Path diagram showing the influence of age, genetic (A), and environmental (C and E) factors on height, MAP, and AI (Cholesky decomposition). The observed phenotypes are shown in squares, and latent factors are shown in circles. Factor loadings of observed variables on the different latent factors are represented by the arrows. For clarity, only 1 twin of a pair is shown, and arrows loading on the latent factors A and C are omitted.

phenotypes are shown in squares, and latent factors are shown in circles. Factor loadings of observed variables on the different latent factors are represented by the arrows. Factor loadings for the last factor (A4, C4, E4) reflect influences specific to AI and can be represented by h_{AI} , c_{AI} , and e_{AI} respectively. The heritability of AI corrected for the influence of height, MAP, and age can be calculated as follows: $h^2_{cor} = h^2_{AI} / (h^2_{AI} + c^2_{AI} + e^2_{AI})$.

The genetic correlation (r_g) between 2 traits gives an indication of the amount of overlap between (sets of) genes influencing those traits. r_g is calculated as the (additive) genetic covariance (COV_A) between 2 traits divided by the square root of the product of the total genetic variance components of each of the traits. The genetic correlation between, for example, MAP and AI therefore equals $r_g = COV_A(MAP, AI) / \sqrt{(V_{MAP} * V_{AI})}$.

Shared and unique environmental correlations are calculated in a similar fashion.

Model Fitting

A series of submodels nested within the full-parameter Cholesky model were fitted to the multivariate variance-covariance matrices. The significance of variance components A, C, D, and age was assessed by testing the deterioration in model fit after each component was dropped from the full model, leading to a model in which the pattern of variances and covariances is explained by as few parameters as possible. Submodels were compared with the full model by hierarchical χ^2 tests. The difference in χ^2 values between submodel and full model is itself approximately distributed as χ^2 , with degrees of freedom (df) equal to the difference in df of submodel and full model. Model selection was also guided by Akaike's information criterion ($AIC = \chi^2 - 2df$). The model with the lowest AIC reflects the best balance between goodness of fit and parsimony.

Statistical Software

Data handling and preliminary analyses were done with STATA.⁴¹ Univariate and multivariate quantitative genetic modeling were performed with Mx.⁴²

Results

General Characteristics

Fifty twin pairs (12 MZ and 38 DZ) were excluded from the final analysis. In at least 1 twin of 47 pairs (51 individuals or 3.1% of the cohort), an arterial waveform could either not be obtained or the measurement was of insufficient quality. Three pairs were excluded, of which 1 twin had an extremely low, and presumed erroneous, AI (<4 SD below the mean).

TABLE 1. Characteristics of MZ and DZ Twin Pairs of the Study Sample

Characteristic	MZ	DZ
No. of pairs	213	556
Age, y	46.0 (14.3)	45.2 (11.6)
AI, %	21.0 (14.8)	21.0 (14.0)
Central SBP, mm Hg	110.4 (18.6)	110.7 (16.7)
Peripheral SBP, mm Hg	119.6 (18.8)	120.0 (16.8)
DBP, mm Hg	76.7 (12.5)	77.7 (11.7)
MAP, mm Hg	92.4 (14.8)	93.0 (13.5)
Pulse pressure, mm Hg*	44.3 (11.7)	43.7 (10.5)
Heart rate, bpm	72.5 (11.1)	73.1 (11.3)
Height, m	1.63 (0.06)	1.63 (0.06)
Weight, kg	64.6 (10.2)	66.6 (12.8)
BMI, kg/m ²	24.4 (4.0)	25.2 (4.7)
Menopausal, %	43.0	36.9
Antihypertensive medication, %	7.5	5.2
Oral antidiabetic medication, %	0.9	0.1

Values are mean (SD), unless stated otherwise. BMI indicates body mass index.

*Pulse pressure = peripheral SBP - peripheral DBP.

Thus, the total number of twin pairs included in the final analysis was 213 MZ and 556 DZ pairs (1538 subjects).

General characteristics of the twins who were included in the final analyses are shown in Table 1. Characteristics were very similar in the 2 zygosity groups. Results after exclusion of all pairs of which at least 1 twin was on either antihypertensive or hypoglycemic medication (Table 1) were virtually identical to those of the entire group. The results presented here are therefore based on the entire group.

Univariate Analysis

For all measures, intraclass correlations in MZ twin pairs were larger than those in DZ twin pairs, indicating substantial genetic influences on all traits. This pattern was confirmed by the univariate model fitting. Parameter estimates of the best fitting univariate models and their 95% CI are shown in Table 3. The heritability of AI was estimated at 37%, whereas age explained 19% of the variance. In the best model for AI, C could be dropped without a deterioration in fit ($\chi^2[1]=0.0$; $P=1.0$), ie, the contribution of shared environment to AI was not significant.

TABLE 2. Intraclass Correlations for MZ and DZ Twin Pairs

Measure	MZ	DZ
AI, %	0.61	0.33
Central SBP, mm Hg	0.60	0.42
Peripheral SBP, mm Hg	0.55	0.40
DBP, mm Hg	0.49	0.33
MAP, mm Hg	0.55	0.35
Pulse pressure, mm Hg	0.41	0.26
Heart rate, bpm	0.45	0.35
Height, m	0.89	0.57

TABLE 3. Parameter Estimates and 95% CIs of the Best-Fitting Univariate Models (Based on AIC)

Measure	h ²	95% CI	c ²	95% CI	e ²	95% CI	Age ²	95% CI
AI, %	0.37	0.22–0.44	0.44	0.37–0.52	0.19	0.15–0.23
Central SBP, mm Hg	0.18	0.00–0.37	0.16	0.02–0.30	0.46	0.39–0.55	0.20	0.18–0.24
Peripheral SBP, mm Hg	0.17	0.00–0.38	0.18	0.03–0.33	0.51	0.43–0.60	0.14	0.10–0.18
DBP, mm Hg	0.22	0.00–0.44	0.15	0.00–0.31	0.54	0.46–0.65	0.09	0.06–0.12
MAP, mm Hg	0.25	0.03–0.45	0.12	0.00–0.28	0.50	0.42–0.59	0.13	0.09–0.17
Pulse pressure, mm Hg	0.13	0.00–0.37	0.14	0.00–0.29	0.65	0.55–0.75	0.08	0.05–0.11
Heart rate, bpm	0.23	0.00–0.46	0.23	0.06–0.40	0.54	0.45–0.65
Height, m	0.60	0.50–0.72	0.25	0.14–0.35	0.12	0.10–0.15	0.03	0.01–0.05

h² indicates heritability; c², shared environmental variance component; e², unique environmental variance component; and age², variance component due to influence of age.

For all BP variables (including heart rate), a full ACE model was chosen as the best model, on the basis of the lowest AIC. Although this method of model selection led to a consistent picture for all BP traits with ACE models providing the most realistic explanation of the data, for several BP traits, h², c², or both were not always strictly significant, ie, the CI included zero (see Table 3). Heritabilities ranged from 13% to 25% in the BP variables, whereas shared environment and age explained 12% to 18% and 8% to 20% of the variance, respectively. No influence of age on heart rate was found. Height showed the expected large genetic component (60%) and a somewhat smaller influence of shared environment (25%).

Multivariate Analysis

Values of phenotypic correlations (n=1538) were as expected: AI was positively correlated with age (r=0.44) and MAP (r=0.33) and negatively with heart rate (r=-0.28). Taller women had a lower AI (r=-0.21), most likely due to later wave reflection from more distant peripheral reflecting sites.^{15,16,24}

Results of the multivariate model fitting, including height, heart rate, MAP, AI, and age, are shown in Table 4. Both hierarchical χ^2 tests and AIC values indicated that the ACE model including age showed the best fit to the data. Neither C nor A could be dropped from the full ACE model because both the AE ($\chi^2[10]=37.0$; $P<0.001$) and the CE model ($\chi^2[10]=123.2$; $P<0.001$) showed a significant deterioration in fit. There was no indication of a dominant genetic influence because the ACE model showed a better fit to the data than the ADE model. The influence of age could not be dropped from the ACE model without a significant reduction in fit ($\chi^2[4]=318.2$; $P<0.001$).

TABLE 4. Results of Multivariate Model Fitting

Model	χ^2	df	P	AIC
ACE*	67.67*	55*	0.12*	-42.33*
ACE without age	385.87	59	0.00	267.87
ADE	104.05	55	0.00	-5.95
AE	104.67	65	0.00	-25.33
CE	190.89	65	0.00	60.89

Apart from the ACE without age model, all models included age.
*Most parsimonious solution.

Parameter estimates of the best-fitting multivariate model are not shown because they were virtually identical to the univariate parameter estimates. Moderate genetic correlations between AI and MAP (r_g=0.38), AI, and heart rate (r_g=-0.38) and between AI and height (r_g=-0.29) were found. Unique environmental correlations for the same pairs of variables were smaller, with values of 0.15, -0.32, and -0.02. These results indicate that the phenotypic correlations between especially AI and MAP and AI and height are predominantly due to shared genes influencing these traits.

Sources of variance in AI are shown in Table 5. The last column lists the amount of variance in AI explained by age, height, heart rate, MAP, and AI specific factors. Each of these sources of variance is additionally decomposed in genetic, shared, and unique environmental factors. In the best-fitting multivariate model, 36.5% of the variance in AI was determined by genetic factors, of which 5.6% was due to genes in common with MAP, 4.6% to genes in common with heart rate, and 3.1% to genes in common with height. Approximately 44% was due to unique environmental variation, of which 2.6% was due to environmental influences in common with MAP and 4.6% in common with heart rate. The contribution of shared environment to AI was negligible. It is clear from Table 5 that most of the total phenotypic variance in AI (60.2%) is explained by genetic and unique environmental factors specific to AI, with height (3.1%), heart rate (9.5%), and MAP (8.4%) contributing only relatively small parts of the variance. The remaining variation in AI (18.8%) could be attributed to the effect of age. The heritability of AI adjusted for age, height, heart rate, and MAP equalled the following: $h^2_{cor} = 0.232 / (0.232 + 0.0 + 0.37) = 0.38$.

TABLE 5. Sources of Variance in AI Based on Best-Fitting Multivariate Model

Source of Variance	h ²	c ²	e ²	Age ²	Total
Age	18.8	18.8
Height	3.1	0.0	0.0	...	3.1
Heart rate	4.6	0.3	4.6	...	9.5
MAP	5.6	0.2	2.6	...	8.4
AI specific	23.2	0.0	37.0	...	60.2
AI total	36.5	0.5	44.2	18.8	100.0

Values are percentages. For abbreviations, see Table 3.

Discussion

This study quantified genetic and environmental sources of variance in AI and investigated to what extent these were dependent on the effects of age, height, heart rate, and BP. Furthermore, it was estimated how much of the variation in central and peripheral SBP, MAP, DBP, pulse pressure, and heart rate was due to genetic factors. To our knowledge, our study is the first to report heritabilities of AI, central SBP, and pulse pressure and is the largest twin study that measured SBP and DBP.^{18,43,44} AI was used as the primary end point in our study because it is an index of pulsatile load and may help to elucidate the genetic basis of hemodynamic mechanisms contributing to hypertrophy of the left ventricle. Total heritability of AI was higher (37%) than the heritabilities for the BP traits, which varied between 13% and 25%. Most of the variance in AI could be explained by genetic and environmental factors specifically influencing AI. Although AI had some genes in common with MAP and height, as evident from the genetic correlations, only a relatively small part of the total variance in AI could be attributed to these genes: 3.1%, 4.6%, and 5.6% for height, heart rate, and MAP, respectively. A considerable portion of the total variation in AI could be explained by age (18.8%), confirming the importance of the effect of aging on systolic augmentation.^{8,15,23} The heritability of AI adjusted for age, height, and MAP (38%) was highly similar to the unadjusted heritability (37%). The absence of a common environmental effect on AI indicates that influences due to a shared family environment in childhood (eg, dietary influences) have little bearing on AI in later life.

The heritability estimates for central SBP and pulse pressure were both relatively small but similar to the estimate for peripheral SBP. Interestingly, age had a larger effect on central than on peripheral SBP, which may reflect the larger effect of aging on systolic augmentation.²³ It may also be related to the greater amplification of the pulse between central and peripheral arteries in the more compliant arterial system of youth. As the arteries stiffen with age, amplification decreases, and central pressure more closely approximates peripheral pressure.⁴⁵

Intraclass correlations for the BP-related variables were as high as one would expect for traits showing a considerable amount of intraindividual variation. Intraclass correlations for peripheral SBP and DBP were very similar to those reported in earlier studies, although heritability estimates in our study were somewhat lower.^{18–22,43,44} One reason for this difference may be that twin studies have little power to discriminate between additive genes or shared environment as sources of familial resemblance unless a multivariate approach is used.^{22,46} Earlier twin studies on BP were substantially smaller than our study and therefore lacked the power to detect a shared environmental component, which may have led to inflated estimates of heritability. Even with a twin study of our size, we had difficulty in making the distinction between additive genes and shared environment in univariate analyses of the BP traits. Another reason for the lower heritability estimates in our study may be the incorporation of age as a variance component in the model. We decided to incorporate age because, if unaccounted for, it can spuriously introduce a common environmental effect.³⁹ We would have observed higher heritabilities if we had either

ignored the effect of age or had performed the model-fitting analysis using age-adjusted BP values.

Several potential sources of bias may have had an influence on our results. Medication use is unlikely to have had an effect on the model-fitting results since these remained unchanged after exclusion of twins using antihypertensive and hypoglycemic medication. The mean values of general characteristics of MZ and DZ twins in this study were very similar. Only weight and the percentage of postmenopausal twins showed some slight differences between zygosity. Neither weight nor menopausal status was significantly associated with AI in a multiple regression after the inclusion of age (data not shown). Therefore, these minor differences between MZ and DZ twins are unlikely to have biased the results for AI.

The reported results are likely to be representative of the general population because basic characteristics of the twins were similar to a population-based sample of women participating in the Chingford cohort study in London.⁴⁷ Furthermore, mortality of adult twins has been shown to be similar to that of the general population.⁴⁸ However, since they were limited to women, the results of our study cannot be generalized to men. Hayward and Kelly¹⁵ observed that from an early age, AI was higher in women than in men. This is most likely related to more prominent wave reflection due to shorter stature in women, rather than due to gender differences in arterial stiffness, since women have been shown to have a more compliant arterial tree, at least until the menopause.⁴⁹ Future twin studies aimed at systematically investigating gender differences in genetic influences on AI should include opposite-sex twin pairs in addition to same-sex male twins.⁵⁰

Our estimate of heritability for AI provides a yardstick against which the contribution to AI of either candidate genes or novel loci can be evaluated. Since AI is thought to be a composite of arterial stiffness (determined by the structural components of the arterial wall) and wave reflection from peripheral sites, any gene influencing these pathways may be considered a candidate for AI. A fruitful strategy to detect novel loci may be to measure, in addition to AI, 1 or more related traits, for example, pulse wave velocity in a large number of unselected sib pairs or DZ twins for use in a genome screen. AI and pulse wave velocity may be influenced by a common set of genes, which would offer prospects for gene finding since it has been shown that multivariate genetic modeling increases the power to locate pleiotropic quantitative trait loci.⁵¹

In summary, AI has a significant genetic component, which is largely independent of the influence of BP, height, and age. Finding genes for AI could help to unravel pathophysiological mechanisms causing left ventricular hypertrophy and may lead to improvements in prevention, diagnosis, and treatment of at-risk populations.

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