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Measurement of heritability of myocardial blood flow by positron emission tomography: the Twins Heart Study

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Abstract

Objective—To estimate the heritability of myocardial blood flow (MBF) and coronary flow reserve (CFR) measured with positron emission tomography (PET).

Design—Cross-sectional twin study.

Setting—General clinical research centre of a university hospital at Atlanta, USA.

Patients—A sample of 180 middle-aged (mean±SD 55±2.9 years) male twins, including 107 monozygotic and 73 dizygotic twins.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the institutional review board at Emory University.

Provenance and peer review Not commissioned; externally peer reviewed.

Main outcome measures—All twins underwent imaging of MBF with PET $^{13}\text{NH}_3$ at rest and after adenosine stress during a single imaging session. Structural equation modelling was used to estimate the heritability of MBF at rest and during adenosine stress, as well as of CFR.

Results—The basal MBF (mean \pm SD) was 0.69 \pm 0.20 ml/min/g, and the MBF during adenosine stress was 1.70 \pm 0.49 ml/min/g; the CFR was 2.62 \pm 0.99. There was substantial heritability for MBF both at rest (0.48, 95% CI 0.29 to 0.64) and during adenosine stress (0.51, 95% CI 0.29 to 0.68), as well as CFR (0.48, 95% CI 0.26 to 0.65).

Conclusions—For the first time, a substantial genetic contribution to the interindividual variation in MBF and CFR measured with PET in middle-aged men has been demonstrated. The data suggest that a fruitful direction for future work would be the identification of genetic variants for early atherosclerotic stages assessed by PET imaging.

INTRODUCTION

Atherosclerosis is a process that may begin early in life, but may not become clinically manifest until atherosclerotic plaques reach a critical stage.¹ Early identification and preventive treatment for asymptomatic coronary artery disease (CAD) can potentially reduce the risk of subsequent overt CAD. Recent studies have indicated that abnormalities in the function and structure of the coronary microcirculation (small vessels <200 μm) may represent an early atherosclerotic stage.² Because no technique allows the direct visualisation of coronary microcirculation in vivo in humans, its assessment relies on the measurement of functional variables, such as myocardial blood flow (MBF).³ Positron emission tomography (PET) myocardial perfusion imaging combined with tracer-kinetic modelling affords the non-invasive quantification of regional blood flow.⁴ Reduced coronary flow reserve (CFR), defined as the ratio of hyperaemic-to-basal coronary flow velocity, in the absence of obstructive coronary stenoses is a marker of coronary microvascular dysfunction.³

A number of CAD traditional risk factors have been linked to coronary microvascular dysfunction, including smoking, hypertension, hyperlipidaemia and diabetes.² Since genetic factors play important roles in atherosclerosis,⁵ it may also be possible that genetic variations contribute to MBF and CFR. A positive family history of CAD has been related to impaired regulation of coronary blood flow in humans,⁶ and several candidate genes have been associated with CFR.^{7–9} To date, however, little is known about the familial or genetic basis of MBF and CFR. Recently, a study in rats has shown a significant genetic component for CFR, with 62% of total phenotypic variance attributable to genetic variance.¹⁰ However, no heritability estimation has been reported in humans.

The variance of MBF and CFR in a population is due to genetic and environmental factors. Since families share both genes and environment, it is difficult to separate out the effects of each. Twin studies provide a unique opportunity to examine the relative importance of genetic and environmental influences on a phenotype. Because identical or monozygotic (MZ) twin pairs share the same genes, and non-identical or dizygotic (DZ) twins share on average half of their segregating genes, a greater phenotypic similarity in MZ twins than DZ twins suggests genetic influences on that trait.¹¹ Factors such as perfect age matching and

more similar early familiar environment allow twin studies to calculate an accurate genetic contribution to a trait—that is, the heritability. The goal of this classic twin study is to estimate the genetic and environmental influences on MBF and CFR measured with PET in middle-aged male twins.

MATERIALS AND METHODS

Subjects

Twins included in the Twins Heart Study (THS) were selected from the Vietnam Era Twin Registry, which consists of 7369 middle-aged male–male twin pairs both of whom served in the US military during the time of the Vietnam War.¹²

The THS included 180 twin pairs (93 monozygotic and 87 dizygotic), who were born between 1946 and 1956. The methods of construction of this sample have been described elsewhere.¹³ In brief, two groups of twin pairs were randomly sampled from the Vietnam Era Twin Registry: (1) twin pairs who were discordant for major depressive disorder (MDD); (2) pairs where neither had a history of MDD. Once selected, twin pairs came together, but were examined separately, at the Emory University General Clinical Research Center between March 2002 and March 2006, where they had a comprehensive physical examination. In a previous study, we reported a significant association between MDD and CFR.¹³ To avoid the potential influence of MDD on biometric genetic modelling of CFR, only the 105 twin pairs without MDD were included in the present analysis. The protocol was approved by the institutional review board at Emory University, and informed consent was obtained from all subjects.

MBF measurement using PET

Twins underwent imaging of MBF with PET $^{13}\text{NH}_3$ at rest and after pharmacological (adenosine) stress during a single imaging session. PET data were collected as described in our previous study,¹³ as well as in the online supplementary material. Our main outcome was the overall measure of CFR for the entire myocardium, defined as the ratio of maximum flow during stress to flow at rest. The subject's heart rate and blood pressure were monitored to calculate the rate–pressure product (RPP) as an index of cardiac work. Because resting MBF may be related to cardiac work, to account for individual differences, we corrected resting blood flow for the main determinants of external cardiac workload (ie, RPP), by multiplying the subject's rest blood flow by the mean RPP of the study population and dividing the result by the subject's RPP.¹⁴ Accordingly, a corrected CFR was defined as the ratio of adenosine-induced flow to RPP-corrected resting flow; this correction accounted for variations in resting myocardial oxygen demand.

Other measurements

A medical history and a physical examination were obtained from all twins. Weight and height were used to calculate the body mass index (BMI). Cigarette smoking was classified into current versus never or past smoker. Pack-years of smoking were calculated as the number of packs of cigarettes smoked per day multiplied by the number of years smoked. Physical activity was assessed with a modified version of the Baecke Questionnaire of

Habitual Physical Activity¹⁵; this is a 16-question instrument documenting level of physical activity at work, during sports and non-sports activities. The global physical activity score was used in the analysis. Direct high-density lipoprotein (HDL) and direct low-density lipoprotein (LDL) cholesterol were obtained using homogeneous assays (Equal Diagnostics, Exton, Pennsylvania, USA). Glucose was measured on the Beckman CX7 chemistry autoanalyser. Diabetes was defined as having a fasting glucose level >126 mg/dl or being treated with anti-diabetic medication. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg, or current pharmacological treatment for hypertension. History of CAD was defined as previous myocardial infarction, angina pectoris or coronary revascularisation procedures.

Statistical analysis

In initial descriptive analyses, we compared means (or prevalence) of MBF and other study variables between MZ and DZ twins. To improve the distributional properties of MBF, rest MBF, hyperaemic MBF and CFR were log-transformed. Correlations between blood flow and other cardiovascular risk factors were assessed using Pearson correlations for continuous risk factors and Spearman correlations for categorical risk factors. Generalised estimating equations were used to correct for the correlation between co-twins. Analyses were performed using Stata V.8.

Structural equation modelling (SEM) was used to obtain estimates of the genetic and environmental influences on MBF and CFR.¹⁶ The assumptions under twin modelling are that MZ twins share 100% of their genes, whereas DZ twins share, on average, 50% of their genes. Shared environmental factors are assumed to be 100% for both MZ and DZ twins if siblings were reared together, as in our sample, while unique environment is not shared between the siblings for either MZ or DZ twins. Thus, a greater phenotypic similarity in MZ twins than DZ twins suggests genetic influences on that trait. Model fitting 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) genetic components and shared (C) or unique (E) environmental components. The ratio of additive genetic variance (A) to total phenotypic variance (A+C+E) is defined as heritability (h^2).

A series of SEM models were fitted. The significance of A, C and E was tested by removing them sequentially in specific submodels and comparing these with the full model. Standard likelihood-ratio tests between models were used to assess the importance of each variance component (A, C or E) on the fit of the model, leading to a model in which the pattern of variance–covariance is explained by as few variables as possible. Another statistic, the Akaike's Information Criterion (AIC), was also used to determine the optimal model fitting, where a lower AIC indicates a more parsimonious, and thus a better fitting, model.

The heritability was estimated using the most parsimonious SEM model. To examine whether the genetic contributions to blood flow were independent of other covariates, we repeated the heritability estimation after adjusting for covariates that showed an association with measures of blood flow at a p value <0.10. These include BMI, LDL cholesterol, HDL cholesterol, DBP and current smoking. Age was always included in the model. The analyses

were also repeated after exclusion of the subjects with a history of CAD. All genetic model fitting was carried out with the Mx statistical program.¹⁷

RESULTS

Of the 210 THS twins (105 pairs) without a lifetime history of MDD, 30 were excluded because of missing PET data, leaving 180 for the analysis (including 52 MZ pairs, 34 DZ pairs and eight unpaired twins). The mean age (\pm SD) was 55 years (\pm 2.85), with a range of 47–60 years. Thirty-two subjects (17.8%) were current smokers. A small number of twins ($n=11$, 6.1%) had diabetes, while the number with hypertension was large ($n=77$, 42.3%). About 8% of twins ($n=15$) had a history of CAD. Table 1 shows the demographic characteristics and CAD risk factors in MZ and DZ twins. For all study factors, there were no significant differences according to zygosity.

Haemodynamic data and blood flow are shown in table 2. The resting MBF corrected for RPP was 0.689 ± 0.20 ml/min/g, and the hyperaemic MBF was 1.702 ± 0.49 ml/min/g. The mean RPP-corrected CFR was 2.62 ± 0.99 . Heart rate at rest was higher in DZ than MZ twins, but there were no significant differences in resting blood pressure and RPP. Resting MBF corrected for RPP and MBF during adenosine infusion was also similar between MZ and DZ twins, as well as CFR corrected for RPP.

The correlations between MBF and traditional cardiovascular risk factors are shown in the online supplementary table. Resting MBF was significantly associated with BMI and DBP ($p < 0.05$), and borderline associated with HDL cholesterol ($p < 0.10$). No risk factor was significantly associated with MBF during stress. For CFR, a significant positive correlation was found with BMI ($p=0.02$), and borderline correlations were found with smoking (inverse) and LDL cholesterol (positive) ($p < 0.10$). All p values are derived from generalised estimating equations taking into account intra-pair correlations. These covariates, including age, BMI, LDL cholesterol, HDL cholesterol, DBP and smoking, were then adjusted for in the heritability estimation analysis of blood flow.

For both MBF at rest and during stress, as well as CFR, the correlations in MZ twins were consistently higher than those in DZ twins, indicating genetic influence (table 3). This was confirmed by genetic modelling. The best fitting models for all traits included only genetic (A) and unique environmental (E) contributions. Common environmental influences were not significant for MBF or CFR. For all three traits, the heritability estimations were ~50%, with the remaining variation due to unique environmental influences. After adjustment for covariates, the heritability estimates were slightly decreased, but the overall results remained similar. Additional adjustment for pack-years and use of drugs such as statins did not change the results. Heritability estimations were also similar after exclusion of the 15 subjects with a previous history of CAD.

DISCUSSION

An impairment in coronary circulatory function reflects a proatherosclerotic state, with considerable diagnostic and prognostic implications.²³ We demonstrated a substantial

genetic contribution to the interindividual variation in MBF and CFR measured with PET in middle-aged men.

The underlying causes of coronary circulatory dysfunction are multifactorial. Coronary flow is regulated by the oxygen demand of the myocardium and involves a number of complex metabolic, endothelial and neural mechanisms.¹⁸ Some studies suggest that adenosine-induced hyperaemic coronary flow (and CFR) not only occurs through vascular smooth muscle relaxation, but also represents endothelium-dependent vasodilation.¹⁹ The endothelium releases several vasoactive substances with relaxing or constricting vascular smooth muscle effects.¹⁹ Several CAD risk factors that are known to impair endothelial function, including smoking, hyperlipidaemia, diabetes and hypertension, are associated with coronary micro-vascular dysfunction.² Oxidative stress may be another pathway.²⁰ Other active processes are probably involved, such as inflammation, smooth muscle cell proliferation, and the expression of vascular cellular adhesion molecules.²¹ These processes may initiate and contribute to the development and progression of atherosclerosis, and may explain the independent predictive role of coronary circulatory dysfunction for future cardiovascular events.²³

In addition to traditional CAD risk factors, genetic variation may also contribute to the development of CAD. Previous twin studies have found that coronary heart disease deaths, myocardial infarction and angina pectoris have a substantial hereditary component.^{22,23} Most recently, advances in bioinformatics and high-throughput genomic technology have facilitated the completion of several genome-wide association studies (GWAS) to search for susceptibility genes for CAD.²⁴ A number of loci have been consistently identified through GWAS and follow-up studies, including genes that regulate known risk factors (eg, lipid metabolism), but also genes involved in as yet unknown metabolic pathways. For example, the most robust genetic risk variant is located on chromosome 9p21.3, which is a region without a known protein-encoding gene, but contains a large antisense non-coding RNA gene (ANRIL) that affects the regulation of other genes.²⁵ These GWAS findings have been recently reviewed by Girelli *et al.*²⁴ Although these genetic variants may drive the discovery of novel biological mechanisms involved in the pathophysiology of CAD, they explain only a fraction of the heritable component of CAD and have little predictive value of an individual's risk of cardiovascular events.²⁶ Identification and evaluation of important intermediate phenotypes of CAD may reduce heterogeneity and be helpful in genetic studies.²⁷ Intermediate phenotypes that are early indicators of CAD, such as microvascular function measured by means of CFR, may be particularly informative in this respect.

Our data showing substantial heritability of MBF and CFR measured with PET suggests that genetic variants are involved in early atherosclerosis and microvascular dysfunction. The heritability estimates were similar for MBF at rest and during stress. However, further analysis revealed that different genes may influence these two phenotypes. We constructed a bivariate twin model and found that there was no shared genetic component between these two traits, indicating that independent genes may be involved in the regulation of MBF at rest and during stress (data not shown). These results are also substantiated by the absence of a significant phenotypic correlation between rest and stress MBF (Pearson correlation $R = -0.07$, $p = 0.34$). To date, only a few candidate genes have been investigated, which are

involved in the pathways of endothelial function,⁷ oxidative stress⁸ and lipid profile.⁹ Some of the genes were associated with hyperaemic blood flow and CFR,⁷⁸ while some were associated with MBF at rest only.⁹ Our findings of independent heritability between rest and hyperaemic MBF were consistent with these preliminary data. Moreover, a recent randomised, placebo-controlled study showed that lipid-lowering therapy for 6 months with pravastatin improved CFR in young subjects with mild hypercholesterolaemia, but that this effect was modulated by apolipoprotein E genotype,²⁸ suggesting a potential gene–environment interaction in the regulation of coronary blood flow. However, because of the complex genetic and environmental basis of atherosclerotic disease, these reported associations need to be replicated in other, possibly larger, samples.

There are some limitations to our study. First, our sample is derived from a twin registry of military veterans, therefore the generalisation to other populations is not known. Second, since our analyses included only men, generalisation to female populations should be made with caution. Third, in the present analysis, all twins were free from MDD, and this exclusion may affect the heritability estimation of CFR. However, since the prevalence of MDD in the general male population is only about 6%,²⁹ this potential bias should be modest. Finally, our results were derived from predominantly healthy middle-aged adult twin subjects, and therefore may not be extendable to younger or older subjects, or populations with clinically manifest cardiovascular disease. Previous studies have observed impaired CFR in patients with CAD.³⁰ In the present study, a total of 15 subjects with a history of CAD were included in the analysis. There was no significant difference in MBF and CFR between the subjects with and without CAD. To correct for the potential confounding of CAD in the heritability estimate for MBF and CFR, we adjusted for the history of CAD as a covariate. The heritability was similar before and after adjustment. Furthermore, we repeated the analysis after excluding these 15 twins, and the results remained similar.

In summary, we found a substantial heritability of MBF and CFR measured with PET in middle-aged men. Our data provide direction for future studies looking to identify genetic variants for early atherosclerotic stages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Cardiovascular risk factors in the Twins Heart Study subjects according to zygosity

Cardiovascular risk factor	Monozygotic twins (N=107)	Dizygotic twins (N=73)	p Value [*]
Age, years	54.7±2.9	54.9±2.7	0.50
Body mass index, kg/m ²	28.6±4.3	30.1±5.1	0.07
Low-density lipoprotein cholesterol, mg/dl	126.5±32.2	118.1±33.0	0.18
High-density lipoprotein cholesterol, mg/dl	37.4±8.8	40.3±9.5	0.10
Systolic blood pressure, mm Hg	132.3±14.6	131.1±16.9	0.68
Diastolic blood pressure, mm Hg	83.2±11.6	79.9±10.3	0.12
Physical activity, Baecke score	7.45±1.4	7.52±1.4	0.74
Pack-years	15.2±21.3	14.6±18.8	0.91
Current smoker, n (%)	17 (15.9)	15 (20.6)	0.50
Diabetes, n (%)	5 (4.7)	6 (8.2)	0.44
Hypertension, n (%)	46 (43.0)	31 (42.5)	0.96
Coronary artery disease, n (%)	7 (6.5)	8 (10.9)	0.54
Taking ace-inhibitors, n (%)	10 (9.4)	10 (13.7)	0.45
Taking β -blockers, n (%)	9 (8.4)	2 (2.7)	0.26
Taking aspirin, n (%)	26 (24.3)	19 (26)	0.82
Taking statins, n (%)	23 (21.5)	14 (19.2)	0.69

Values are mean±SD or number (%)

* p Values are derived from generalised estimating equations taking into account intra-pair correlations.

Table 2

Haemodynamic data and coronary blood flow according to zygosity

Variable	Monozygotic twins (N=107)	Dizygotic twins (N=73)	p Value*
Heart rate at rest, beats/min	60.6±8.8	64.5±10.0	0.02
Systolic blood pressure at rest, mm Hg	131.7±20.7	130.1±19.6	0.64
Diastolic blood pressure at rest, mm Hg	78.7±11.9	77.8±11.7	0.63
Rate–pressure product at rest [†]	80.4±20.3	83.8±17.9	0.32
Rest flow [‡] , ml/min/g	0.699±0.23	0.674±0.13	0.78
Stress flow, ml/min/g	1.726±0.47	1.681±0.53	0.47
Coronary flow reserve [‡]	2.63±0.9	2.61±1.1	0.73

Values are mean±SD.

* p Values are derived from generalised estimating equations taking into account intra-pair correlations.

[†]Rate–pressure product = (heart rate × systolic blood pressure)/100.

[‡]Corrected by resting rate–pressure product.

Table 3

Intraclass correlations of MZ and DZ twins and heritability estimation for coronary blood flow

	ICC		Heritability (95% CI)	
	MZ	DZ	Unadjusted	Adjusted*
Ln rMBF [†]	0.57	0.16	0.48 (0.29 to 0.64)	0.48 (0.28 to 0.64)
Ln sMBF	0.48	0.34	0.51 (0.29 to 0.68)	0.48 (0.25 to 0.65)
Ln CFR [†]	0.50	0.29	0.48 (0.26 to 0.65)	0.42 (0.18 to 0.61)

* Adjusted for age, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diastolic blood pressure and smoking.

[†] Corrected by rate–pressure product.

CFR, coronary flow reserve; DZ, dizygotic; ICC, intraclass correlation; Ln, natural logarithm; MZ, monozygotic; rMBF, myocardial blood flow at rest; sMBF, myocardial blood flow during stress.