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Genetic Factors are Important Determinants of Impaired Growth Following Infant Cardiac Surgery

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Abstract

Objectives—To estimate the prevalence and identify the predictors of impaired growth following infant cardiac surgery.

Methods—Secondary analysis of a prospective study of the role of apolipoprotein E (*APOE*) gene polymorphisms on neurodevelopment in young children following infant cardiac surgery. Prevalence estimates for growth velocity were derived using anthropometric measures [weight (WT) and head circumference (HC)] obtained at birth and at 4-years of age. Genetic evaluation was also performed. Growth measure *z*-scores were calculated using World Health Organization Child Growth Standards. Growth velocity was evaluated using two different techniques: first by clustering the children into one of three growth velocity subgroups based on *z*-score: impaired growth (difference < −0.5 SD), stable growth (difference of −0.5 SD to 0.5 SD), and growth improving (difference > 0.5 SD), and, second, using continuous difference scores. Statistical analyses were conducted using a combination of proportional odds models for the ordered categories and simple linear regression for the continuous outcomes.

Results—Three hundred and nineteen full term subjects had complete anthropometric measures for WT and HC at birth and at 4-yrs. The cohort was 56% male. Genetic examinations were available for 97% (309/319) of the cohort (normal, 74% definite or suspected genetic abnormality, 26%). Frequency counts for WT categories were: impaired growth 37% stable growth 31% and improving growth 32%. Frequency counts for HC categories were: impaired growth 39% stable growth 28% and improving growth 33%. Presence of a definite or suspected genetic syndrome (*p* = 0.04) was found to be a predictor of impaired growth for WT, but not HC. When growth *z*-

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scores were used as continuous outcomes, the *APOE* $\epsilon 2$ allele was found to be predictive of lower z-scores for both WT ($p = 0.02$) and HC ($p = 0.03$).

Conclusions—Impaired growth for both WT and HC is common (both > 30%) in this cohort of children following infant cardiac surgery. Both the *APOE* $\epsilon 2$ allele and the presence of a definite or suspected genetic syndrome were associated with impaired WT growth velocity. The *APOE* $\epsilon 2$ allele was also associated with impaired growth velocity for HC. Persistent poor growth may have long-term implications for the health and development of children with CHD.

Keywords

Heart Defects, Congenital; Genetic Predisposition to Disease; Apolipoproteins E; Growth Impairment

Introduction

Optimal growth during early childhood is important for normal development. Sub-optimal growth may lead to decreased survival and poor cognitive outcomes. Chronic disease states increase the risk of growth impairment. Despite early neonatal repair and improved survival of children with CHD, there is increasing evidence that children with congenital heart defects (CHD) are at an increased risk for both impaired growth and abnormal neurodevelopment.(1-5) Growth impairment in children with CHD may begin prior to birth as indicated by an increased prevalence of intra-uterine growth retardation in several population-based studies.(6-8) During the perioperative period, altered energy intake and energy expenditure result in an ongoing risk of malnutrition. (9-14) The prevalence and etiology of growth impairment in the CHD population is poorly understood. Simple cross-sectional analyses of growth using group means or simple thresholds for adequate growth are relatively insensitive and may fail to identify many children with impaired growth.(15) Assessment of growth patterns or velocity may be more appropriate in children with chronic diseases who are at an increased risk for poor growth. (16-18) Identification of children with impaired growth is important as inadequate nutritional intake and subsequent poor growth are potentially modifiable factors. Therapeutic interventions which lead to more optimal growth may result in improved outcomes.

In 1998, we initiated a prospective study evaluating the association between neuro-developmental dysfunction and apolipoprotein-E (*APOE*) genotype in 550 neonates and infants undergoing surgery for CHD. *APOE* is an important regulator of cholesterol metabolism and has an important role as a susceptibility gene that modifies outcome following central nervous system (CNS) injury. The *APOE* $\epsilon 2$ allele was associated with significantly worse neuro-developmental outcomes at 1 and 4-years of age. (19,20) Anthropometric growth measurements were obtained from labor and delivery records and at both these evaluations. The current study was undertaken to estimate the prevalence and identify predictors of impaired growth from birth to 4-years of age following infant cardiac surgery.

Methods

Study Population

The study constitutes a secondary analysis of a subgroup of a prospective study of the role of *APOE* gene polymorphisms on neurodevelopment following cardiac surgery in infancy. (19,21) Patients ≤ 6 months of age undergoing surgery for CHD using cardiopulmonary bypass (CPB) with or without deep hypothermic circulatory arrest (DHCA) were eligible. Exclusion criteria were: 1) multiple congenital anomalies, 2) recognizable genetic or

phenotypic syndrome other than chromosome 22q11 microdeletion syndrome, and 3) language other than English spoken in the home. Patients underwent neurodevelopmental assessments at 1 and 4-years of age. The current study evaluated full-term infants (gestational age ≥ 37 weeks) for whom complete birth and 4-year data on relevant anthropometric measures were available. Premature infants were excluded because the World Health Organization (WHO) growth chart normative data does not include premature infants. The study was approved by the Institutional Review Board at The Children's Hospital of Philadelphia. Informed consent was obtained from the parent or guardian.

Operative Management

Surgery was performed by five cardiac surgeons with a dedicated team of cardiac anesthesiologists. Alpha-stat blood gas management was utilized. Pump flow rates were not standardized for this study. DHCA was utilized at the surgeon's discretion. Prior to DHCA, patients underwent core cooling, with topical hypothermia of the head, to a nasopharyngeal (NP) temperature of 18 °C. Modified ultrafiltration was performed in all patients.

Anthropometric Measurement and Growth Assessment

Anthropometric measurements [weight (WT) and head circumference (HC)] were obtained at birth and at a four year follow-up. Of note both length and height were obtained at birth and the four year respectively, however the birth length measurement was considered not sufficiently accurate to use for an analysis where the focus was on patterns of growth after cardiac surgery. Birth measurements were collected from labor and delivery records. Measurements at the 4-year follow-up were obtained by research nurses using standardized research protocols with digital scales and stadiometers. WT for age z -scores (WAZ) and HC for age z -scores (HCZ) were calculated using the World Health Organization (WHO) Child Growth Standards. The WHO Growth Standards were released in 2006 and are based on a prospectively collected data from a population of ethnically diverse singleton term born infants who were primarily breastfed. This population was selected to represent optimal growth; that is "how children should grow". (22) Use of the WHO standards provides adjustment for growth differences due to gender and ethnicity.

Genetic Evaluations

Patients were evaluated at the 1 and/or 4-year evaluations by a genetic dysmorphologist. Chromosome analysis and testing for microdeletion of 22q11 were performed as indicated. Results of the genetic evaluations were classified as *normal* if no genetic or chromosomal abnormality was demonstrated, *abnormal* if a specific diagnosis was confirmed, and *suspect* if there was evidence of a genetic syndrome that could not be confirmed. For the analysis, the abnormal and suspect subgroups were combined.

APOE Genotype Determination

Whole blood or a buccal swab was obtained before the operation and stored at 4°C. Genomic DNA was prepared and used to determine *APOE* genotypes using a previously published method. Subjects were grouped by *APOE* genotype into the $\epsilon 2$ group ($\epsilon 2\epsilon 2$ and $\epsilon 3\epsilon 2$), the $\epsilon 3$ group ($\epsilon 3\epsilon 3$), and the $\epsilon 4$ group ($\epsilon 3\epsilon 4$ and $\epsilon 4\epsilon 4$). The $\epsilon 2\epsilon 4$ subjects were excluded from the analyses because the $\epsilon 2$ and $\epsilon 4$ alleles are opposing in their effects in some conditions, such as Alzheimer disease. (19)

Cardiac Diagnosis

Cardiac diagnosis was coded according to a previously described classification incorporating anatomy and perioperative physiology that has been shown to be predictive of perioperative mortality. (23) Class I is 2 ventricles with no aortic arch obstruction, Class II is

2 ventricles with aortic arch obstruction, Class III is single ventricle with no arch obstruction, and Class IV is single ventricle with arch obstruction. Patients with tetralogy of Fallot (TOF) and transposition of the great arteries are in Class I, whereas patients with hypoplastic left heart syndrome (HLHS) or variants are in Class IV.

Data Analysis and Statistical Methods

Data analysis proceeded in three discrete phases: first, a descriptive phase in which traditional descriptive statistics were computed for all variables in the data set, with a particular emphasis on growth status at birth and 4-years of age; and, second, a prevalence phase, in which prevalence estimates for impaired growth were computed using two different criteria: (a) a simple cross-sectional evaluation using a cutoff of -2 SD for WT and HC z-scores at four years of age, and (b) by using an estimate of growth velocity from birth to four years (z-score at birth minus z-scores at four years). Growth velocity categories were created by sub-dividing the z-score difference values into three different velocity subgroups: impaired growth (difference < -0.5 SD), stable growth (difference of -0.5 SD to 0.5 SD), and growth improving (difference > 0.5 SD). The importance of using both criteria is that the cross-sectional evaluation with a -2 SD threshold is a traditional screening criterion for growth failure in the healthy populations. Use of growth velocities allows evaluation of the pattern and tempo of growth and will identify those children who have deviated substantially from their individual growth trajectories.

In the risk modeling phase, a total of 14 separate single covariate proportional-odds growth failure models were specified and tested using the three velocity subgroups as the outcome, and a selected set of patient-specific and peri-operative variables as the testable covariates. Finally, four single covariate linear regression models were also tested in which the original continuous measure of velocity (z-score at birth minus z-score at 4-years) served as the outcome and genotype and duration of DHCA at the first operation were used as the testable covariates. In an effort to rule out the possibility of redundancy among predictors, the relationship between duration of DHCA and cardiac diagnosis was estimated using a Spearman-rho correlation coefficient. Due to the exploratory nature of the study, alpha was not adjusted beyond the traditional $\alpha = 0.05$ level. All data were analyzed using SAS v9.1.

Results

Between September 1998 and April 2003, 675 eligible infants underwent cardiac surgery. Twenty-three infants died prior to consent, parents of 102 declined participation and 550 (81%) were enrolled. There were 21 deaths during the initial hospitalization and an additional 43 prior to 5-years of age. Four hundred and eighty-six patients were alive and eligible for the 4-year evaluation, which was completed by 381 patients (78% of eligible). Baseline characteristics have been previously reported for patients returning for the 4 year evaluation ($n = 381$), those who did not return ($n = 105$), and those who died before age 4 years ($n = 64$). The only significant difference in baseline characteristics between returning and non-returning patients was under-representation of African-Americans in the returning patients (21% vs. 29%). Three hundred and nineteen patients met entry criteria for the current study. Baseline characteristics are shown in Table I.

Prevalence of Impaired Growth

Cross-Sectional Evaluation—The mean WAZ at birth and four years of age were -0.14 (± 1.12) and 0.21 (± 1.17), respectively. The mean HCZ at birth and four years were -0.19 (± 1.37) and -0.28 (± 1.22), respectively. The prevalence of impaired growth as assessed by a WAZ ≤ -2.0 was 5% at birth and 6% at four years. The prevalence of impaired growth as assessed by a HCZ ≤ -2.0 at birth was 9% at birth and 8% at four years.

Growth Velocity—Frequency counts for growth velocity groups for WT were: impaired growth 37% (117/319), stable growth 31% (100/319), and improving growth 32% (102/319). Frequency counts for growth velocity subgroups for HC were: impaired growth 39% (126/319), stable growth 28% (88/319), and improving growth 33% (105/319).

Risk Models

Weight Growth Velocity Categories—Presence of a definite or suspected genetic syndrome was a predictor of impaired growth for WT, $p = 0.04$. (Table II) Longer duration of DHCA was also associated with impaired WT growth, $p = 0.02$. Duration of DHCA was related to the cardiac diagnosis, $r = 0.57$, $p < 0.001$. Use and longer duration of DHCA were more common in Class IV patients. Overall, cardiac diagnosis was not associated with WT growth. However, growth impairment for WT was more common in Class IV patients compared to Class I patients, $p = 0.01$. *APOE* genotype was not associated with WT growth.

Head Circumference Growth Velocity Categories—Presence of a definite or suspected genetic syndrome, longer duration of DHCA, and cardiac diagnosis were not predictive of HC growth. (Table III) Overall, *APOE* genotype was not associated with HC growth. However, growth impairment for HC was more common in patients with the *APOE* $\epsilon 2$ allele compared to those with the $\epsilon 3$ allele, $p = 0.037$.

Growth Velocities as Continuous Outcomes—The *APOE* $\epsilon 2$ allele was predictive of lower growth velocity for both WT ($p = 0.02$) and HC ($p = 0.03$). Longer duration of DHCA at the first operation was also associated with lower growth velocity for both WT ($p = 0.01$) and HC ($p = 0.02$). However the r^2 for both was approximately 0.02, suggesting that most of the variance for both WT and HC, up to 98%, is not explained by these factors.

Discussion

Growth patterns provide an important window into the overall well-being of healthy children and those with chronic diseases. In this study, we show that growth impairment or faltering assessed as a declining growth velocity between birth and 4-years for both WT and HC is common (both $> 30\%$) following infant cardiac surgery. Evaluation of growth using more traditional criteria such as group means or use of cross-sectional assessment with a simple threshold was relatively insensitive and suggested a much lower prevalence of growth impairment (6-8%). Use of growth velocities identifies subnormal WT or HC rate of gain rather than merely subnormal WT or HC. (15) Defining growth impairment as falling below a pre-determined percentile or z-score is only an estimate of attained weight not an estimate of growth because it will not identify children who fall from a high percentile or z-score. Use of the growth velocities shows that children with CHD are a heterogeneous population with differing patterns of growth. In addition to the impaired growth subgroup, there is a group with improving or increasing growth velocity. While some of these children may be exhibiting “catch-up” growth; others may be at risk for childhood obesity.

In the current study, we identified both the *APOE* $\epsilon 2$ allele and the presence of a definite or suspected genetic syndrome were associated with impaired WT growth velocity. The *APOE* $\epsilon 2$ allele was also associated with impaired growth velocity for HC. In addition, longer duration of DHCA at the initial operation was associated with impaired growth as assessed by body weight. However, taken in combination, these factors explain only a very small portion ($< 2\%$) of the variability in growth for both WT and HC. No other factors were found to be predictive of either impaired or improving growth.

The large group of patients with impaired HC growth is particularly concerning. Neurodevelopmental dysfunction is now the most common, and potentially disabling, long-

term complication of CHD and its treatment. Infancy and early childhood are critical periods for brain growth. Early post-natal malnutrition is associated with significantly retarded central nervous system growth, reduced brain weight, thinner cerebral cortex, and deficient myelination. (24) The adverse effects of malnutrition on neurodevelopmental outcomes have been well described in other population. Inadequate nutritional intake and subsequent poor growth are potentially modifiable factors. Early identification of patients at risk for poor growth could lead to therapeutic interventions, more optimal growth, and improved neurodevelopmental outcomes.

Impaired growth has long been recognized as a significant problem in children with CHD. In 1962, Mehrizi and Drash called attention to the common occurrence of growth disturbances in children with a wide variety of CHD. (25) Levy and associates evaluated growth in patients with ventricular septal defects (VSD) enrolled in the Joint Study on the Natural History of Congenital Heart Defects. (1) Successful surgery resulted in a significant increase in weight but not height. Medical therapy was associated with little change in the subnormal growth pattern. They concluded that the severe growth disturbance in patients with VSD is only in part due to abnormal postnatal hemodynamics. Intrauterine and genetic factors and low birthweight were identified as risk factors and might explain the incomplete growth response after successful surgery. A subsequent study of long-term growth of children with CHD showed that growth in children with a large VSD or TOF was abnormal. Growth improved but did not normalize after surgery. (4) More recently Cheung and associates demonstrated normalization of long-term growth after repair of TOF. (26) More recently there has been increased interest in growth patterns for on patients with single ventricle anatomy and physiology. Cohen and colleagues found that children with functionally univentricular hearts who have been palliated with a Fontan operation are significantly underweight and shorter than the general population and their siblings. (27) In a more recent study, Vogt and coworkers found that impaired growth is common in children with single ventricle physiology prior to completion of the superior cavopulmonary connection and that some “catch-up” growth occurred subsequently. (28) However, even after the Fontan procedure, the median WAZ remained decreased at -0.7 . The findings of these studies are consistent with the current study in identification of more complex CHD and genetic factors as important risk factors for growth disturbance. Unlike the current study, these studies used group means to estimate the prevalence of growth failure. The current study demonstrates that group means and screening thresholds are insensitive measures which fail to identify many children with impaired growth.

The etiology of growth failure in patients with CHD is multifactorial and most likely includes a hypermetabolic state, inadequate caloric intake, malabsorption, genetic factors, or a consequence of fluid restriction as part of hemodynamic intervention. (10-13) Inadequate caloric intake is probably a major contributor to growth failure in neonates who require cardiac surgery. (13) Feeding difficulties are common in this population and may be due to congestive heart failure, vocal cord paresis, uncoordinated sucking and swallowing, fatigue, or feeding aversion. (12) In addition, digestion and absorption in the gastrointestinal tract can be impaired by gut edema. Patients with single-ventricle physiology and an aortopulmonary shunt may have relative splanchnic ischemia due to diastolic runoff from the shunt and are at increased risk for necrotizing enterocolitis. (13)

APOE polymorphisms might have different roles during early development and aging. (29,30) In adults, the *APOE* $\epsilon 4$ allele is associated with a risk of Alzheimer disease and worse outcome after traumatic brain injury. (31) However, there is evidence that infants with the *APOE* $\epsilon 4$ allele may have advantages over those with the *APOE* $\epsilon 2$ and $\epsilon 3$ alleles with respect to early life neuronal and brain development. (32) We have shown that the *APOE* $\epsilon 2$ allele was associated with significantly worse neuro-developmental outcomes at 1 and 4-

years of age.(19,20) In the current study, we found that the *APOE* ϵ 2 allele is also associated with a risk of impaired WT and HC growth. In addition, there is evidence that early cognitive development under the stresses of environmental factors such as malnutrition and lead exposure may be modulated by *APOE* genotype. (29,30,32) As in the current study, the *APOE* ϵ 2 allele is associated with worse outcomes, while the *APOE* ϵ 4 allele is protective. This finding is consistent with the concept of thrifty genotypes and thrifty phenotype; metabolic adaptations adopted as survival strategies by a malnourished fetus or infant which may be inappropriate to deal with a later life of affluence. (33) The *APOE* ϵ 4 allele is a more lipid-thrifty variant that is more efficient in sequestering cholesterol and raising serum lipid levels, which might have a critical role for brain development and maturation.(29,30,33) While this phenomenon may be advantageous in an infant with marginal nutrition, it is associated with hyperlipidemia and coronary artery disease in adults. (31)

There are several limitations to this study. The birth data were collected from delivery room records and thus measurements may not have been made in a standard fashion. Anthropometric data are available for only two time-points. We did not collect parental anthropometric data to determine if a small child is constitutionally small. However, use of growth velocity obviates some of this problem as a child who is small and has a decline of 0.5 z-score still exhibits poor growth. Finally, regression to the mean must always be considered as a potential influence when multiple measures are obtained over time. Yet, regression to the mean is generally symmetric and is as likely to happen for low scoring children as it is for high scoring children. Even in the presence of regression to the mean, however, children tend to remain around their expectation (i.e., their expected levels of performance), with some fluctuation both ways. Hence, fluctuation associated with regression to the mean is not unidirectional. In the current sample of children undergoing surgery for heart disease, we simply don't see the same proportion of children at the high ends of the distributions that we saw at the low ends, especially with respect to growth failure. We do, however, have a fairly high number of infants who scored low initially and then remained "within their growth channel" relative to the WHO standards at birth and four years of age.

In summary, impaired weight and head circumference growth as assessed by declining growth velocities is common following cardiac surgery in infancy. The significant prevalence of impaired head growth is particularly concerning because of the implications for neurodevelopmental outcomes. Growth velocities are more appropriate and sensitive measures of growth patterns than simple cross-sectional evaluations. Genetic factors are important determinants of impaired growth. However, the risk factors identified in this study explain only a small portion of the variability in outcomes, suggesting that many thus far unidentified factors likely contribute to the risk of poor growth. Nutritional support of children with CHD is a modifiable factor. Early identification of patients at risk for poor growth could lead to therapeutic interventions, more optimal growth, and improved neurodevelopmental outcomes. Further research is needed to assess risk factors for poor growth, evaluate the impact of poor growth on neurodevelopmental outcomes, and determine the role for therapies to improve nutrition and growth.

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Abbreviations

APOE Apolipoprotein E

CPB	Cardiopulmonary bypass
CHD	Congenital heart defects
DHCA	Deep hypothermic circulatory arrest
HC	Head Circumference
HCZ	HC for age z-scores
NP	Nasopharyngeal
SD	Standard deviation
TOF	Tetralogy of Fallot
VSD	Ventricular Septal Defect
WT	Weight
WAZ	WT for age z-scores
WHO	World Health Organization

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Table I
Baseline and Operative Characteristics

	Entire Group	Impaired Growth	Stable Growth	Improving Growth
Number	319	117 (37%)	100 (31%)	102 (32%)
Gender				
Female	139 (44%)	47 (40%)	53 (53%)	39 (38%)
Male	180 (56%)	70 (60%)	47 (47%)	63 (62%)
Ethnicity				
Asian-Pacific, Hispanic, Other	34 (11%)	13 (11%)	12 (12%)	9 (9%)
African-American	68 (21%)	16 (14%)	20 (20%)	32 (31%)
Caucasian	217 (68%)	88 (75%)	68 (68%)	61 (60%)
Diagnostic Class				
I: Two Ventricles/ no arch obstruction	163 (51%)	53 (46%)	51 (51%)	59 (58%)
II: Two Ventricles/ arch obstruction	43 (14%)	12 (10%)	18 (18%)	13 (13%)
III: One Ventricle/ no arch obstruction	29 (9%)	12 (10%)	5 (5%)	12 (12%)
IV: One Ventricle/ arch obstruction	84 (26%)	40 (34%)	26 (26%)	18 (17%)
Genetic Evaluation				
Normal	237 (74%)	78 (67%)	79 (79%)	80 (78%)
Yes	82 (26%)	39 (33%)	21 (21%)	22 (22%)
APOE Genotype				
ε2	30 (10%)	15 (13%)	9 (9%)	6 (6%)
ε3	187 (60%)	63 (55%)	57 (60%)	67 (67%)
ε4	92 (30%)	36 (32%)	29 (31%)	27 (27%)
Missing	10	3	5	2
DHCA First OP				
No	135 (42%)	41 (35%)	43 (43%)	51 (50%)
Yes	184 (58%)	76 (65%)	57 (57%)	51 (50%)
Additional OPs Prior to 4 Year Evaluation				
None	189 (59%)	60 (51%)	63 (63%)	66 (65%)
1-2	122 (38%)	55 (47%)	35 (35%)	32 (31%)
>2	8 (3%)	2 (2%)	2 (2%)	4 (4%)

Table II
Risk Models for Weight Growth Velocity Categories (Logistic Regression)

Parameter	Estimate	Standard Error	Pr > ChiSq
Confirmed or Suspected Genetic Anomaly	-0.242	0.121	0.045
Diagnostic Class			0.060
Class II vs. I	0.163	0.235	0.489
Class III vs. I	0.110	0.273	0.674
Class IV vs. I	-0.475	0.193	0.014
<i>APOE</i> Genotype			0.12
<i>APOE</i> ϵ 2 vs. <i>APOE</i> ϵ 3	-0.392	0.244	0.107
<i>APOE</i> ϵ 4 vs. <i>APOE</i> ϵ 3	0.064	0.178	0.718
Duration CPB 1 st Operation	0.001	0.003	0.629
Duration Additional CPB	-0.002	0.002	0.238
Duration DHCA 1st Operation	-0.011	0.005	0.017
Duration Additional DHCA	-0.005	0.004	0.284

Table III
Risk Models for Head Circumference Growth Velocity Categories (Logistic Regression)

Parameter	Estimate	Standard Error	Pr > ChiSq
Confirmed or Suspected Genetic Anomaly	-0.095	0.120	0.430
Diagnostic Class			0.40
Class II vs. I	-0.269	0.239	0.260
Class III vs. I	0.250	0.274	0.361
Class IV vs. I	-0.138	0.192	0.471
<i>APOE</i> Genotype			0.099
<i>APOE</i> ϵ 2 vs. <i>APOE</i> ϵ 3	-0.519	0.249	0.037
<i>APOE</i> ϵ 4 vs. <i>APOE</i> ϵ 3	0.224	0.180	0.213
Duration CPB 1 st Operation	0.001	0.003	0.581
Duration Additional CPB	-0.001	0.002	0.493
Duration DHCA 1 st Operation	-0.008	0.005	0.092
Duration Additional DHCA	0.002	0.004	0.648