

## Patterns of Prenatal Growth among Infants with Cardiovascular Malformations: Possible Fetal Hemodynamic Effects

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This study characterized fetal growth differences among control infants ( $n = 276$ ) and infants with d-transposition of the great arteries (TGA) ( $n = 69$ ), tetralogy of Fallot ( $n = 66$ ), hypoplastic left heart syndrome ( $n = 51$ ), and coarctation of the aorta ( $n = 65$ ), thus permitting assessment of competing theories about the relation between these cardiovascular malformations and fetal growth disturbance. Subjects were liveborn singletons without genetic or extra-cardiovascular structural abnormalities sampled from the Baltimore-Washington Infant Study. Multivariate analysis of covariance was performed: birth weight, birth length, newborn head circumference, and two nonlinear functions of these measures were regressed jointly on a diagnostic class variable and covariates. Differences in the vectors of dependent variable means across diagnostic groups were striking ( $p < 0.0001$ ). Infants with TGA had normal birth weight, but lesser head volume relative to birth weight. Infants with tetralogy of Fallot were smaller in all measured dimensions, but they were shaped normally. Infants with hypoplastic left heart syndrome were smaller in all measured dimensions, and head volume was disproportionately small relative to birth weight. Infants with coarctation of the aorta had lower birth weight, shorter birth length, and greater head volume relative to birth weight. These findings suggest that fetal circulatory abnormalities may predict abnormal patterns of fetal growth. *Am J Epidemiol* 1996;143:505-13.

anthropometry; birth weight; fetal growth retardation; heart defects, congenital; hemodynamics

Consistent, often strong, associations between the presence of congenital cardiovascular malformations and low birth weight or intrauterine growth retardation have been reported over several decades in clinical and pathologic case series, as well as in population-based studies (1-13). The Baltimore-Washington Infant Study demonstrated persistence of the associations between most prevalent cardiovascular malformations and birth weight deficits following adjustment for important confounding variables (10). A review of the literature uncovered no population-based studies of congenital cardiovascular malformations that have addressed diagnostic group-specific differences in birth length, newborn head circumference, or anthropometric indices derived from these routine newborn measures. Carlgren (4) reported birth length deficits, and Stoll et al. (9) found both birth length and head circumference deficits among neonates considered col-

lectively with many forms of cardiovascular malformations.

The nature of the associations between cardiovascular malformations and fetal growth impairment remains a mystery, but two competing explanations (14, 15) seem most plausible. Embryos with intrinsic growth disturbances may be at increased risk for developmental errors during cardiogenesis (14). Alternatively, fetal circulatory patterns in the presence of specific cardiovascular malformations may be incompatible with optimal fetal growth (15). Evaluation of these possibilities is complicated by our limited understanding of cardiac teratogenesis and fetal circulatory changes in the presence of specific cardiovascular malformations.

To our knowledge, the present study is the first to evaluate and characterize the extent and pattern of fetal growth differences between controls and affected infants with either d-transposition of the great arteries (TGA), tetralogy of Fallot, hypoplastic left heart syndrome, or coarctation of the aorta. These malformations offer unique contrasts in both proposed teratogenic processes (16-21) and proposed fetal circulatory disturbances (table 1) (22), thus allowing insight into the nature of the associations between these cardiovascular malformations and intrauterine

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Abbreviations: SE, standard error; TGA, d-transposition of the great arteries.

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TABLE 1. Fetal hemodynamic abnormalities anticipated with specific cardiovascular malformations\*

| Diagnostic group | Volume, direction of flow in vessel† |             |                   |              | Oxygen saturation in vessel‡ |              |                    |
|------------------|--------------------------------------|-------------|-------------------|--------------|------------------------------|--------------|--------------------|
|                  | Ascending aorta                      | Aortic arch | Ductus arteriosus | Distal aorta | Aortic arch                  | Distal aorta | Pulmonary arteries |
| TGA‡             | N, →                                 | N, →        | N, →              | N, →         | ↓↓                           | ↑            | ↑                  |
| TF‡              | ↑, →                                 | ↑, →        | ↓, ←              | N, →         | ↓                            | ↓            | ↑                  |
| HLH‡             | ↓↓, ←                                | ↓, ←        | ↑, →              | ↑, →         | ↓                            | ↓            | ↑                  |
| CA‡              | ↓, →                                 | ↑, ←        | N, →              | ↓, →         | N                            | N            | N                  |

\* Heterogeneity within diagnostic groups is surely present. These predicted effects are based on expected differences in resistance to flow and intracardiac mixing using the method of Heymann and Rudolph (22).

† N, normal; ↑, increased; ↓, decreased; ↓↓, greatly decreased; →, antegrade; ←, retrograde.

‡ TGA, transposition of the great arteries; TF, tetralogy of Fallot; HLH, hypoplastic left heart syndrome; CA, coarctation of the aorta.

growth impairment through epidemiologic investigation.

This study evaluates fetal growth among infants who do not have identified genetic or extra-cardiovascular structural abnormalities ("isolated" cases). The study hypothesis is that fetal growth in infants with these isolated cardiovascular malformations is different from that in controls, as reflected in the multivariate distributions of birth weight, birth length, head circumference, ponderal index, and power index (described in "Statistical Methods"). Observed differences in fetal growth are reconciled with proposed teratogenic mechanisms and proposed fetal circulatory disturbances to explore the nature of the associations between specific cardiovascular malformations and fetal growth disturbance.

## MATERIALS AND METHODS

### Subjects and data

All subjects included in the Fetal Growth Study were previously enrolled in the Baltimore-Washington Infant Study (1983-1987) (23), a population-based, case-control study designed to explore environmental and genetic etiologic risk factors for congenital cardiovascular malformations. Cases include all infants who were born with cardiovascular malformations, who were liveborn to residents of Maryland, Washington, DC, and northern Virginia, and who were diagnosed prior to one year of age. Cases were ascertained from multiple sources: all regional pediatric cardiology centers, vital statistics records, the pathology logs of the 52 area hospitals, and regional medical examiners. Cardiovascular malformation diagnoses for all cases were confirmed by echocardiography, catheterization, surgery, or autopsy. Infants with more than one cardiovascular malformation were assigned a principal diagnosis corresponding to the lesion manifested earliest in cardiogenesis. Diagnostic categories reflect the principal diagnosis of affected infants. Controls are a representative sample of the birth cohort to which the cases belonged, selected randomly follow-

ing stratification by hospital of birth. Each hospital contributed a proportion to the sample of controls equal to the proportion it contributed to the birth cohort of the study region (23).

Mothers of all Baltimore-Washington Infant Study subjects were interviewed at home by trained interviewers soon after ascertainment using a standardized questionnaire to obtain information on demographic and socioeconomic factors, family and reproductive histories, environmental exposures, and birth weight and gestational characteristics (23). Specifically, the Baltimore-Washington Infant Study contributed data on cardiovascular diagnosis and maternal prepregnancy weight, weight gain, and smoking status. For Fetal Growth Study subjects, anthropometric, pregnancy, and delivery data were retrieved from the medical records of both the infant and the mother. The birth weight, birth length, newborn head circumference, date of the mother's last menstrual period, estimated date of confinement, infant sex and race, and maternal diabetic status were abstracted from the hospital records of the study subjects and mothers (24).

Singleton infants without genetic or extra-cardiovascular structural abnormalities were selected from subjects enrolled after April 1, 1983 for inclusion in the sampling frame for cases and controls in the Fetal Growth Study. The 26 birth hospitals that contributed most eligible cases were chosen as record abstraction sites. In order to maximize sample sizes, all eligible cases born in the selected hospitals were included in the Fetal Growth Study. Approximately 70 percent of eligible cases with the four diagnoses of interest were selected by this sampling strategy. One control (whose birth date was closest to that of the case) was selected from each birth hospital for every case born at that hospital. The medical records for approximately 92 percent of cases and 97 percent of controls included in these samples were available for review. The final sample sizes were: TGA,  $n = 69$ ; tetralogy of Fallot,  $n = 66$ ; hypoplastic left heart syndrome,  $n = 51$ ;

coarctation of the aorta,  $n = 65$ ; and controls,  $n = 276$  (24).

### Statistical methods

In addition to the abstracted anthropometric measures, two nonlinear indices were computed from these measures (see Appendix for computational formulas) and included in the analysis to evaluate differences in infant shape. The ponderal index provided information about relative thinness (25). The power index provided information about head volume relative to birth weight (26).

Gestational age was computed using the abstracted last menstrual period whenever this was available (87.9 percent). When an abstracted last menstrual period was not available, the gestational age was computed using either the last menstrual period obtained from the study questionnaire (3.4 percent) or the abstracted estimated date of confinement (8.7 percent). Gestational age was rounded to the greatest completed week.

For the primary analysis, a single multivariate analysis of covariance was performed using a general linear models procedure (see Appendix for details of the model) (27). The set of five dependent variables considered jointly consisted of birth weight, birth length, head circumference, ponderal index, and power index. This analysis was selected for its ability to optimally discriminate anthropometric differences across diagnostic groups while taking into consideration important dependencies among the anthropometric variables.

Maternal weight gain, smoking, prepregnancy weight, and diabetes mellitus, and infant sex, race, and gestational age were included as covariates in the model to adjust for confounding and to improve precision. Diagnostic category and gestational age were treated as classification variables. Multivariate interactions between diagnostic categorization and each covariate were evaluated using cross-product terms to determine whether diagnostic group-specific differences in vectors of means were dependent on specific values of the covariates. The omnibus  $F$  test of the four indicator variables for diagnostic class was used to test the null hypothesis that, adjusted for the main covariates, all diagnostic categories had the same vector of dependent variable means.

To assess fetal growth differences between specific diagnostic groups and controls (after adjusting for the covariates), the contrast between each diagnostic group and controls was highlighted. Each contrast yielded a single eigenvalue with a unique eigenvector (proportional to a constant), which allowed diagnostic group-specific differences in the joint distributions of

the dependent variables to be demonstrated and tested. Thus, four statistical tests were performed, one for each contrast. The null hypotheses stated that the vector of dependent variable means in each diagnostic group is equal to the vector of means in the control group. The Bonferroni correction was used to control overall Type I error in this analysis, yielding a corrected critical value of 0.0125 for rejecting any one of the four null hypotheses while preserving an overall Type I error rate at 0.05 (28).

The remaining analyses were exploratory, and formal hypothesis testing was not performed. These analyses elaborated the intricacies of the diagnostic group-specific differences in neonatal anthropometry within multivariate and univariate frameworks. Multivariate exploratory analyses permitted assessment of the relative importance of each dependent variable while accounting for diagnostic group-specific differences in the remaining dependent variables. Univariate analyses supported the interpretation of the multivariate analyses.

Each of the four contrasts between individual diagnostic groups and the control group generated a single eigenvector. Each eigenvector represents the axis that best distinguishes the indicated diagnostic group from the control group. Contrast-specific canonical variates defined by these eigenvectors (see Appendix) were correlated with the dependent variables to demonstrate the anthropometric measures and indices most important in distinguishing specific diagnostic groups from the control group. The contrast-specific canonical variates were then regressed on an indicator variable for diagnostic group and the covariates to determine whether affected infants or controls had greater adjusted mean values of the canonical variate. Crude mean values for the anthropometric measures and indices within each diagnostic group are also presented. Finally, each dependent variable was regressed individually on diagnostic class and the set of covariates to generate adjusted mean diagnostic group-specific differences in the univariate distributions of the anthropometric measures and indices.

## RESULTS

### Statistical tests

For the null hypothesis that the vector of means for the dependent variables is constant among the five diagnostic categories after adjustment for the covariates, the omnibus  $F$  statistic was 3.25 (degrees of freedom: 20 (numerator) and 1,648 (denominator)) ( $p < 0.0001$ ).

The  $F$  statistics and nominal  $p$  values corresponding to the hypothesis tests for the contrasts comparing

each diagnostic group with the control group are shown in table 2. In each instance, the null hypothesis of equality across vectors was rejected after the Bonferroni correction was applied, which supports the alternative hypotheses that the vectors of dependent variable means in each diagnostic group differed from the vector in controls. The eigenvectors and eigenvalues for each contrast also are shown in table 2. Coefficients for the correlations between the canonical variates for the eigenvectors and the dependent variables are shown in table 3. Crude means and standard deviations for the anthropometric measures and indices appear in table 4. Differences across diagnostic group in adjusted means for the dependent variables considered individually are shown in table 5.

### Transposition of the great arteries

The canonical variate that best distinguishes infants with d-transposition of the great arteries (TGA) from controls correlated most strongly with the power index and head circumference, and correlated moderately with birth length and ponderal index (table 3). The adjusted difference in this canonical variate indicates that, compared with controls, infants with TGA had smaller head volume given birth weight, smaller head circumference, shorter birth length, and greater birth weight for birth length. (Adjusted control mean - adjusted case mean ( $\Delta$ ) = -0.02990, standard error (SE) = 0.0079).

These findings are consistent with the differences in the crude means of these anthropometric measures and indices that were observed in the exploratory analyses (table 4). As shown in table 5, no apparent difference in adjusted mean birth weight existed between infants with TGA and controls. Adjusted deficits for birth

length and head circumference were approximately 0.5 cm among infants with TGA. Infants with TGA also demonstrated considerable adjusted deficits in head volume relative to birth weight, as well as slightly greater birth weight relative to birth length.

### Tetralogy of Fallot

The canonical variate that optimally distinguishes infants with tetralogy of Fallot from controls correlated very strongly with birth weight, birth length, and head circumference, and much less with the ponderal and power indices (table 3). The adjusted difference in this canonical variate ( $\Delta$  = -0.02939, SE = 0.0067) indicates that smaller values were found among infants with tetralogy of Fallot. Therefore, infants with tetralogy of Fallot had lower birth weight, shorter birth length, and smaller head circumference compared with the controls.

In the exploratory analyses, these differences were apparent in the crude means for the anthropometric measures (table 4). When considered individually, the adjusted differences in the anthropometric measures between infants with tetralogy of Fallot and controls were of remarkable magnitude (table 5). Infants with tetralogy of Fallot demonstrated lower adjusted mean birth weight, birth length, and head circumference. For this malformation, differences in shape parameters were minimal.

### Hypoplastic left heart syndrome

The canonical variate that best distinguished infants with hypoplastic left heart syndrome from controls correlated most strongly with head circumference, birth weight, birth length, and head volume given birth

TABLE 2. Eigenvectors, eigenvalues, and corresponding  $F$  statistics for the  $W_F^{-1}B_H$  matrices\* for the contrasts between the diagnostic and control groups, after adjustment,† Fetal Growth Study, 1983-1989

| Original axis       | Contrast between controls and |          |          |           |
|---------------------|-------------------------------|----------|----------|-----------|
|                     | TGA‡                          | TF‡      | HLH‡     | CA‡       |
| Birth weight        | 0.000160                      | 0.000109 | 0.000254 | -0.000049 |
| Birth length        | -0.14185                      | -0.07465 | -0.02816 | 0.06510   |
| Head circumference  | 0.28262                       | 0.17509  | -0.00638 | -0.16005  |
| Ponderal index      | -1.00827                      | -0.55154 | -0.18999 | 0.45421   |
| Power Index         | -0.01202                      | -0.00817 | 0.00159  | 0.00887   |
| Eigenvalue          | 0.03991                       | 0.03929  | 0.05390  | 0.04134   |
| $F_{d.f.} = 5, 418$ | 3.34                          | 3.28     | 4.51     | 3.46      |
| $p$ value           | 0.0057                        | 0.0064   | 0.0005   | 0.0045    |

\*  $B_H$  is the between-groups sum of squares and cross-products matrix under the null hypothesis (of a common vector of means for the dependent variables).  $W_F$  is the within-groups sum of squares and cross-products matrix.

† Adjusted for gestational age, infant sex and race, and maternal prepregnancy weight, weight gain, smoking, and diabetes mellitus.

‡ TGA, transposition of the great arteries; TF, tetralogy of Fallot; HLH, hypoplastic left heart syndrome; CA, coarctation of the aorta; d.f., degrees of freedom.

**TABLE 3. Coefficients for the correlations between the dependent variables and the canonical variates that optimize the contrasts between the diagnostic and control groups, after adjustment,\* Fetal Growth Study, 1983–1989**

| Dependent variable | Canonical variate for the contrast between controls and |        |       |        |
|--------------------|---|--------|-------|--------|
|                    | TGA†  | TF†    | HLH†  | CA†    |
| Birth weight       | 0.197   | 0.918  | 0.839 | -0.635 |
| Birth length       | 0.358   | 0.855  | 0.643 | -0.495 |
| Head circumference | 0.542   | 0.705  | 0.920 | -0.052 |
| Ponderal index     | -0.304  | 0.150  | 0.304 | -0.259 |
| Power index        | 0.576   | -0.020 | 0.519 | 0.696  |

\* Adjusted for gestational age, infant sex and race, and maternal prepregnancy weight, weight gain, smoking, and diabetes mellitus.

† TGA, transposition of the great arteries; TF, tetralogy of Fallot; HLH, hypoplastic left heart syndrome; CA, coarctation of the aorta.

**TABLE 4. Crude means (standard deviations) for neonatal anthropometric measurements and indices, by diagnostic group, Fetal Growth Study, 1983–1989**

| Diagnostic group | Dependent variable |                   |                         |   |   |
|------------------|--------------------|-------------------|-------------------------|---|---|
|                  | Birth weight (g)   | Birth length (cm) | Head circumference (cm) | Ponderal index (100 g/cm <sup>3</sup> ) | Power index (cm <sup>3</sup> /g <sup>0.6275</sup> ) |
| Controls         | 3,404 (563)        | 51.43 (2.70)      | 34.26 (1.66)            | 2.513 (0.275)                           | 246.0 (23.9)  |
| TGA*             | 3,429 (501)        | 51.25 (2.60)      | 33.92 (1.45)            | 2.565 (0.356)                           | 238.2 (25.0)  |
| TF*              | 3,094 (692)        | 49.78 (3.94)      | 33.52 (2.02)            | 2.498 (0.329)                           | 245.9 (23.9)  |
| HLH*             | 3,112 (639)        | 50.41 (3.12)      | 33.27 (1.88)            | 2.470 (0.280)                           | 237.3 (25.4)  |
| CA*              | 3,205 (751)        | 50.66 (4.26)      | 34.29 (2.39)            | 2.463 (0.303)                           | 257.1 (25.2)  |

\* TGA, transposition of the great arteries; TF, tetralogy of Fallot; HLH, hypoplastic left heart syndrome; CA, coarctation of the aorta.

**TABLE 5. Adjusted\* mean case-control differences† (standard errors) in neonatal anthropometric measurements and indices, by diagnostic group, Fetal Growth Study, 1983–1989**

| Diagnostic group | Dependent variable |                   |                         |   |   |
|------------------|--------------------|-------------------|-------------------------|---|---|
|                  | Birth weight (g)   | Birth length (cm) | Head circumference (cm) | Ponderal index (100 g/cm <sup>3</sup> ) | Power index (cm <sup>3</sup> /g <sup>0.6275</sup> ) |
| TGA‡             | 3.7 (61.8)         | 0.49 (0.39)       | 0.53 (0.23)             | -0.055 (0.044)                          | 8.66 (3.89)   |
| TF‡              | 219.8 (64.3)       | 1.13 (0.38)       | 0.50 (0.22)             | 0.006 (0.043)                           | -1.43 (3.73)  |
| HLH‡             | 272.7 (71.8)       | 0.94 (0.42)       | 1.03 (0.24)             | 0.051 (0.048)                           | 9.90 (4.04)   |
| CA‡              | 170.0 (64.9)       | 0.76 (0.39)       | -0.12 (0.22)            | 0.022 (0.044)                           | -11.52 (3.73)                                       |

\* Adjusted for gestational age, infant sex and race, and maternal weight gain, smoking, diabetes mellitus, and prepregnancy weight using analysis of covariance.

† Adjusted mean in controls minus adjusted mean in cases.

‡ TGA, transposition of the great arteries; TF, tetralogy of Fallot; HLH, hypoplastic left heart syndrome; CA, coarctation of the aorta.

weight (table 3). The adjusted difference in this canonical variate ( $\Delta = -0.04164$ ,  $SE = 0.0084$ ) indicates that infants with hypoplastic left heart syndrome are small in all dimensions, and have especially small head volume for birth weight.

In the exploratory analyses, observed differences in the crude means for these measures and indices support the multivariate findings (table 4). As shown in table 5, infants with hypoplastic left heart syndrome have the greatest adjusted birth weight and head circumference deficits. Infants with hypoplastic left heart syndrome have shorter adjusted mean birth length than

controls, and the greatest deficit in adjusted mean head volume relative to birth weight.

### Coarctation of the aorta

The canonical variate that best distinguished infants with coarctation of the aorta from the control group correlated most strongly with the power index, birth weight, and birth length (table 3). The adjusted difference in this canonical variate ( $\Delta = 0.02966$ ,  $SE = 0.0074$ ) indicated that infants with coarctation of the aorta were more likely to have large head volume for

birth weight, lower birth weight, and shorter birth length than controls.

These findings conform to differences in crude means observed in the exploratory analyses (table 4). Infants with coarctation of the aorta have adjusted mean birth weight and birth length deficits (table 5). Among these infants, mean head circumference is slightly greater than in controls. These differences are reflected in the profoundly increased mean head volume relative to birth weight seen among these infants.

### Covariates

Each of the covariates was a statistically significant predictor of the joint distribution of dependent variables. For the controls, the mean gestational age was 39.2 completed weeks, compared with 38.7 completed weeks for infants with tetralogy of Fallot. No other diagnostic group had a greater difference in mean gestational age. Mean reported maternal weight gain was comparable among the women whose pregnancies resulted in the birth of controls and women who gave birth to infants with TGA and coarctation of the aorta. Mean reported maternal weight gain during pregnancy for the groups with tetralogy of Fallot and hypoplastic left heart were around 0.5 kg and 1.0 kg less than that of control pregnancies, respectively. The means of reported maternal prepregnancy weight among infants with tetralogy of Fallot, hypoplastic left heart, and coarctation of the aorta exceeded that of controls by at least 1.0 kg. The greatest difference was observed for mothers of infants with hypoplastic left heart syndrome, for whom the average prepregnancy weight exceeded that of control mothers by 2.3 kg. A great male predominance was noted among infants with TGA and coarctation of the aorta. Infants with hypoplastic left heart syndrome also had greater male representation than did the control group. Compared with the controls, the infants with tetralogy of Fallot and hypoplastic left heart syndrome were more likely to be nonwhite, and infants with coarctation of the aorta were more likely to be white. The proportion of nonwhite infants in the group with TGA was comparable to the proportion among controls. Maternal diabetes mellitus was recorded in the medical record more commonly as a pregnancy complication among each diagnostic group than among controls, with the most notable excess present among pregnancies yielding infants with tetralogy of Fallot. Thirty-seven percent of mothers who gave birth to infants with hypoplastic left heart syndrome reported smoking during pregnancy, compared with 27 percent of control mothers. Mothers of infants in the other diagnostic groups reported smoking behavior similar to that of control mothers (24).

### DISCUSSION

After extensive evaluation, we found no systematic, diagnostic group-specific distortions that might have arisen from the design and execution of this study (24). The strong possibility exists that these cardiovascular malformations and fetal growth abnormalities are causally related. However, the nature and direction of such a causal pathway is not easily determined.

Growth retardation and disturbed organogenesis are interrelated teratologic outcomes, and each potentially exacerbates the other (29). Evidence that suggests that fetal growth retardation precedes the development of some cardiovascular malformations has been described (30). On the other hand, hemodynamic alterations that are likely to be present in fetuses with cardiovascular defects may disturb growth.

Based on ecologic data, Spiers (14) has argued that embryonic growth retardation increases susceptibility to most congenital malformations. Ultrasound evidence of growth delay among embryos of diabetic mothers during the period of organogenesis supports the plausibility of this argument (30). If such early embryonic growth delay increased the risk of cardiovascular malformation and foreshadowed subsequent growth retardation, a characteristic form of growth retardation might be shared among infants with cardiovascular malformations related by teratogenic mechanism.

However, this study found no consistency between proposed teratogenic mechanisms and patterns of fetal growth disturbance. For both TGA and tetralogy of Fallot, reduced cell number and cell migration abnormalities have been proposed as etiologic mechanisms (20). Generalized hypoplasia or cell migration abnormalities each could cause fetal growth retardation. However, the neonatal anthropometric characteristics in these diagnostic groups were markedly different. Similarly, TGA, hypoplastic left heart syndrome, and coarctation of the aorta may be caused by embryonic flow abnormalities into, within, and from the developing heart (16, 19–21). If embryonic growth abnormalities predispose to these flow abnormalities, a characteristic pattern of neonatal anthropometry might be expected. Again, however, these groups displayed vastly different patterns of fetal growth.

Intuitively, fetal circulatory disturbances might influence neonatal anthropometry. It is not clear which elements in blood are rate-limiting in the fetal growth process, but oxygen saturation has been used as a proxy for other metabolites that support anabolic processes passed to the fetus by the placenta. Although minor perturbations of the circulatory system may be corrected by compensatory mechanisms (31, 32), se-

vere flow disturbance is known to impair growth and development of affected regions (33).

Specific circulatory abnormalities that overwhelm homeostatic mechanisms might correlate with characteristic patterns of fetal growth retardation. If the oxygen content of blood in the systemic circulation is relatively poor, generalized fetal somatic growth impairment would be expected (34). Impaired postnatal growth among children with cyanotic congenital cardiovascular malformations provides support for this position (35, 36). Generalized hypoperfusion might impair fetal growth and result in compensatory water accumulation (37). If oxygen delivery to a specific region is relatively poor, localized growth deficiency would be expected. Similarly, in the absence of qualitative alterations in the blood, relative hypoperfusion of specific regions would be expected to correlate with localized growth deficiency.

If these effects exist, the proposed circulatory disturbances resulting from the cardiovascular malformations under study predict specific patterns of fetal growth impairment. For infants with TGA, the oxygen content of blood serving the head and upper extremities is probably lower than normal, while that to the distal aorta is probably greater (22). If the fetal circulatory disturbances proposed in TGA are correct, growth impairment of the head and upper extremities would be expected, and growth in areas perfused by flow past the aortic isthmus would be normal or increased. These fetal growth patterns were observed: mean head volume was disproportionately small relative to birth weight among infants with TGA, and birth weight was preserved.

The systemic circulations of fetuses with tetralogy of Fallot and hypoplastic left heart syndrome probably contain relatively deoxygenated blood due to intracardiac mixing. Therefore, generalized fetal growth retardation is predicted. For both diagnostic groups, global growth deficiency was profound, as reflected in lower mean values for each anthropometric measurement.

Among fetuses with hypoplastic left heart syndrome, diminished perfusion to superior structures is also likely, because flow in the aortic arch is retrograde and is probably subject to greater resistance (secondary to the smaller arch lumen usually encountered with this defect). Diminished flow to caudal structures is anticipated in infants with coarctation of the aorta, although qualitative abnormalities of the blood are not expected in this group. If flow to superior structures is diminished in fetuses with hypoplastic left heart syndrome and flow to caudal structures is diminished in fetuses with coarctation of the aorta, head growth deficits would be expected in the former case, and weight and lower extremity growth deficits

would be expected in the latter. These fetal growth patterns were observed: infants with hypoplastic left heart syndrome had especially small head volume for birth weight (even after accounting for their global growth retardation), and infants with coarctation of the aorta had diminished birth weight and birth length but normal head circumference (thus, greater head volume for birth weight).

These observations provide some support for the position that cardiovascular malformations cause characteristic fetal growth abnormalities by altering the quality and/or quantity of arterial blood flow to specific regions of the developing fetus. However, it is important to note that the proposed fetal circulatory perturbations remain largely speculative in the absence of quantitative hemodynamic data for affected human fetuses. In the absence of such quantitative data, newborn upper extremity length measurements may further support this theory of fetal hemodynamic effects of fetal growth among infants with TGA, tubular hypoplasia, or coarctation of the aorta.

In summary, abnormal fetal growth patterns were observed among infants with d-transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart syndrome, and coarctation of the aorta. Different mechanisms of growth impairment may be operating within different diagnostic groups. The presence of specific generalized growth abnormalities related to teratogenic mechanism cannot be excluded based on these data. However, fetal hemodynamic effects on growth appear likely, given the close agreement between growth abnormalities predicted by proposed fetal hemodynamics and the fetal growth abnormalities observed among these subjects.

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## APPENDIX

### Infant shape parameters

Ponderal index was calculated from birth weight and birth length using the standard formula described by Rohrer (25), ponderal index ( $100 \text{ g/cm}^3$ ) =  $100(\text{birth weight (g)/birth length (cm)}^3)$ . The power index, a function of head circumference and birth weight, was computed by the method of Good et al. (26), power index ( $\text{cm}^3/\text{g}^p$ ) =  $(\text{head circumference (cm)}^3/\text{birth weight (g)}^p)$ . The natural log of the cube of head circumference was regressed on the natural log of birth weight (and an intercept) using data from controls. The regression coefficient for log birth weight



served as the power coefficient ( $\hat{\beta}$ ) in the exponent of the denominator of power index ( $\hat{\beta} = 0.6275$ ) for all subjects.

**Statistical model**

The multivariate analysis of covariance model was of the form,  $y'_i = x'_i\beta + \epsilon'_i$ , for  $i = 1$  to  $n$  subjects, where  $y'_{i(1 \times 5)}$  is the row vector of the five dependent variables for the  $i$ th subject,  $x'_{i(1 \times 31)}$  is the row vector for the  $i$ th subject of the constant and 30 independent variables (diagnostic class and covariates, with gestational age coded as a classification variable),  $\beta_{(31 \times 5)}$  is the matrix of regression coefficients, and  $\epsilon'_{i(1 \times 5)}$  is the row vector of errors for the  $i$ th subject (38–40).

The expected value of  $\epsilon'_i$  is zero, and each is assumed to be an independent realization from a five-dimensional multivariate normal distribution with mean zero and covariance matrix,  $\Sigma$ .  $\Sigma$  has elements  $\sigma_{j,k}$  with  $\sigma_{j,j} = \text{var}(y_{i,j})$  and  $\sigma_{j,k} = \text{cov}(y_{i,j}, y_{i,k})$ , indexed by the  $i$ th subject and the  $j$ th and  $k$ th dependent variable (40).

$\beta$  is estimated by least-squares criteria, with the  $j$ th column estimated from the multiple regression of the  $j$ th dependent variable on  $X_{(n \times 31)}$ , the matrix of independent variables for all  $n$  subjects with the  $i$ th row  $x'_i$  (38). Let  $Y_{(n \times 5)}$  be the matrix of dependent variables with  $i$ th row  $y'_i$ . Then, the maximum likelihood estimate of  $\beta$  is:  $\hat{\beta} = (X'X)^{-1}X'Y$ . The residual matrix  $E_{(n \times 5)}$  is defined as:  $E = Y - (X\hat{\beta})$ . The unbiased estimator  $\hat{W}_{(5 \times 5)}$  (sample error covariance matrix) of  $\Sigma$ , the population covariance matrix, is given by:  $\hat{W} = (n - g)^{-1}E'E$ , where  $g$  is the number of degrees of freedom due to regression and  $n$  is the number of subjects (40).

The between-groups covariance matrix,  $\hat{\beta}_{(5 \times 5)}$  was computed for each null hypothesis (H) that the vectors of means for the dependent variables were common across diagnostic class after adjusting for the covariates. Let the subscript F denote reference to the full model without H imposed (with diagnostic class and all main covariates included in X), and let the subscript R denote reference to a reduced model under the null hypothesis (without diagnostic class but with all main covariates included in X). Let  $E_F = Y - (X_F\hat{\beta}_F)$ ,  $E_R = Y - (X_R\hat{\beta}_R)$ . Then  $\hat{\beta}_H = (g_F - g_R)^{-1}(E'_R E_R - E'_F E_F)$ , where  $(g_F - g_R)$  equals the number of degrees of freedom associated with the diagnostic class variable(s).

Let the sums of squares and cross-products matrices corresponding to  $\hat{W}_F$  and  $\hat{B}_H$  be represented by  $W_F$  and  $B_H$ ,

respectively, where  $W_F = E'_F E_F$  and  $B_H = (g_F - g_R)\hat{B}_H$ . The matrix  $W_F^{-1}B_H$  serves as the basis for all invariant multivariate test statistics for the hypothesis (40, 41).

Let  $\lambda_1$  be the largest eigenvalue of  $W_F^{-1}B_H$  and let  $v'_1$  be the corresponding eigenvector. Of all linear combinations of  $y_i$ ,  $c_1 \equiv v'_1 y_i$  has the greatest possible ratio of between-groups variance to within-groups variance under the null hypothesis.  $c_1$  is referred to as the first canonical variate for the hypothesis. The value of this greatest ratio of variances is  $\lambda_1$ , which is equal to the univariate  $F$  statistic of  $c_1$ . Each nonzero eigenvalue ( $\lambda_1 > \dots > \lambda_k$ ) of  $W_F^{-1}B_H$  (where  $k =$  the rank of  $W_F^{-1}B_H$ ) has a corresponding eigenvector  $v'_j$  and canonical variate  $c_j$ . Because eigenvectors are unique proportional to a constant, they were scaled to satisfy the conventional constraint,  $v'_k W_F v_k = 1$  (40).

Because the eigenvalues of  $W_F^{-1}B_H$  measure the degree of the separation of diagnostic groups relative to the within-group dispersion by means of the univariate between-to-within-group variance ratio (adjusted for the main covariates), greater eigenvalues of  $W_F^{-1}B_H$  strengthen the evidence against the null hypothesis (40, 41).

**Statistical test**

The Pillai-Bartlett trace was selected as the multivariate test statistic because, among multivariate tests, it is most powerful in the presence of diffuse non-centrality structures and it is most robust to departures from multivariate normality and homoscedasticity (41). Allowance was made for a diffuse non-centrality structure because diagnostic group-specific differences in both size and shape vectors were anticipated. The Pillai-Bartlett trace ( $V$ ) is the sum of the eigenvalues of the matrix  $B_H(B_H + W_F)^{-1}$  (41, 42). Alternatively and equivalently,

$$V = \sum_{k=1}^4 (\lambda_k / \lambda_k + 1),$$

where the  $\lambda_k$  are the eigenvalues of  $W_F^{-1}B_H$ . Pillai's trace can be used to compute a test statistic which approximates the  $F$  distribution,

$$\{V(2N + S)/(S - V)(2M + S + 1)\} \sim F_{S(2M+S+1), S(2N+S)},$$

where  $M = 0.5(|P - D_H| - 1)$ ;  $N = 0.5(D_E - P)$ ;  $S = \min(P, D_H)$ ;  $P = \text{rank of } (B_H + W_F)$ ;  $D_H =$  hypothesis degrees of freedom; and  $D_E =$  error degrees of freedom (43).