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Dilation of the aortic root in children infected with human immunodeficiency virus type 1: The Prospective P²C² HIV Multicenter Study

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Abstract

Background—Vascular lesions have become more evident in human immunodeficiency virus type 1 (HIV)-infected patients as the result of earlier diagnosis, improved treatment, and longer survival. Aortic root dilation in HIV-infected children has not previously been described. This study was undertaken to determine the prevalence of aortic root dilation in HIV-infected children and to evaluate some of the potential pathogenic mechanisms.

Methods—Aortic root measurements were incorporated into the routine echocardiographic surveillance of 280 children of HIV-infected women: an older cohort of 86 HIV-infected children and a neonatal cohort of 50 HIV-infected and 144 HIV-uninfected children.

Results—By repeated-measures analyses, mean aortic root measurements were significantly increased in HIV-infected children versus HIV-uninfected children (*P* values of .04 and .005 at 2 and 5 years of age, respectively, for aortic annulus diameter, sinuses of Valsalva, and sinotubular junction). Heart rate, systolic blood pressure, stroke volume, hemoglobin, and hematocrit were not significantly associated with aortic root size. Left ventricular dilation, increased serum HIV RNA levels, and lower CD4 cell count measurements were associated with aortic root dilation at baseline.

Conclusions—Mild and nonprogressive aortic root dilation was seen in children with vertically transmitted HIV infection from 2 to 9 years of age. Aortic root size was not significantly associated with markers for stress-modulated growth; however, aortic root dilation was associated with left ventricular dilation, increased viral load, and lower CD4 cell count in HIV-infected children. As prolonged survival of HIV-infected patients becomes more prevalent, some patients may require long-term follow-up of aortic root size.

An arteriopathy involving small and medium-sized arteries was described in 1987 by Joshi et al¹ in children with human immunodeficiency virus type 1 (HIV) infection and acquired immunodeficiency syndrome (AIDS). Vascular lesions have become more evident in HIV-infected patients as the result of improved treatment and survival. HIV-infected patients have had aortic or other large-vessel aneurysms requiring surgery,² and there is one case reported of an HIV-infected patient with a ruptured aneurysm of the sinus of Valsalva.³ Dilation of the aortic root has not been previously reported as a characteristic of HIV-infected patients.

The Prospective P²C² HIV Multicenter Study (P²C² HIV Study) was initiated to provide a systematic surveillance of pediatric pulmonary and cardiovascular complications (P²C²) commonly seen in children exposed to maternal HIV infection. Dilation of the aortic root was seen in a number of HIV-infected patients on echocardiograms that were performed serially as part of the P²C² HIV Study. To determine the prevalence of aortic involvement and to assess longitudinal change, routine measurements of the aortic root were added to the P²C² HIV Study protocol. In this report, the prevalence of aortic root dilation in HIV-infected children is assessed, and some of the potential pathogenic mechanisms are evaluated and discussed.

Methods

From May 1990 to January 1994, HIV-infected women and their children were recruited into the P²C² HIV Study at 5 clinical centers located in 4 major metropolitan regions. Institutional review board approval of the protocol was obtained at each site, and appropriate informed consent was satisfied for each study patient. A detailed description of recruitment and retention strategies for the P²C² HIV Study has been published.⁴

The P²C² HIV Study recruited an older HIV-infected cohort (group I) and a neonatal cohort (group II). Group I was composed of children enrolled at >28 days of age with documented vertically transmitted HIV infection. Children born before April 1, 1985, children with a history of sexual abuse, and children with secondary cancer at enrollment were excluded from the study. Group II was composed of infants born to HIV-infected women enrolled during gestation or by 28 days after birth. A randomly selected group of HIV-uninfected children from this cohort was followed throughout the study as a control group.

Maternal HIV status was determined by antibody testing with an enzyme-linked immunosorbent assay and confirmed by Western blotting. HIV infection was diagnosed if a child had two positive HIV cultures, had a positive HIV antibody test at 15 months of age, died of an HIV-associated condition, or had AIDS. Infants with two negative HIV cultures

(one at 5 months of age) or negative HIV serologic results at 15 months of age were considered to be HIV-uninfected.

Diagnostic anatomic echocardiograms and left ventricular function analyses were performed according to the P²C² HIV Study protocol at 10 designated laboratories affiliated with the 5 clinical centers. Echocardiograms were performed upon enrollment into the study and initially at 4-month intervals for all study patients. After determination of HIV status, studies were performed at 4-month intervals for HIV-infected patients and at 6-month intervals for HIV-uninfected patients. The studies were supervised and reviewed by staff pediatric cardiologists at the clinical centers. Before determination of HIV status, all children received chloral hydrate as indicated for sedation during the echocardiogram; subsequently, only HIV-infected children received sedation for echocardiograms.

Routine measurements of the aortic root were added to the protocol midway through the study in October 1995. Children were followed through January 1997. Measurements at the level of the aortic annulus, sinuses of Valsalva, and sinotubular junction (STJ) were obtained from a standard parasternal long-axis view at a point of maximum diameter during the cardiac cycle (generally mid-systole). The aortic annulus diameter was measured at the hinge points of the valve leaflets. Diameter measurements of the sinuses of Valsalva and STJ were made from inner margin to inner margin, perpendicular to the long axis of the ascending aorta. Measurements were made by technologists and physicians blinded to the HIV status of the patients. Measurements of the proximal ascending aorta were not included in the study protocol because of concerns regarding accuracy and reproducibility.

Potential confounding variables for aortic root size were evaluated. Covariate analyses were performed with heart rate, peak systolic blood pressure (BP), stroke volume, hemoglobin, hematocrit, left ventricular end-diastolic dimension (LVEDD), serum HIV RNA level, and CD4 cell count. Heart rate and BP measurements were obtained with the patient supine at the time of the echocardiogram. Systolic and diastolic BP values were recorded as the averages of 3 measurements made with an automated Dinamap vital signs monitor (Critikon, Tampa, Fla). Stroke volume was calculated as LVEDD³ minus left ventricular end-systolic dimension³, with measurements obtained from M-mode strip chart recordings that were digitized at a central echocardiography laboratory. Measurements of hemoglobin and hematocrit were made at 6-month intervals. Serum HIV RNA was assayed by means of a reverse-transcriptase polymerase chain reaction in laboratories according to AIDS Clinical Trials Group quality assurance recommendations. The quantitative polymerase chain reaction was performed with an HIV assay according to the manufacturer's instructions (Amplicor HIV-1 Monitor Test, Roche Diagnostic Systems, Branchburg, NJ).⁵ Lymphocyte phenotypes (CD4 cell counts) were determined in AIDS Clinical Trials Group-certified laboratories, and z-scores were calculated from normal age-adjusted CD4 cell counts from Mofenson et al.⁶

Statistics

Linear and nonlinear regression models were used to examine the relation between aortic root measurements and body surface area (BSA), age, height, and weight with data from 259 normal children measured at a single facility (Children's Hospital, Boston, Mass) in the

same manner as in the study. The two models that best fit the data were a log-log linear regression and a nonlinear power function ($Y = aX^b + c$) with BSA used as the predictor. The quality of the fit for the two models was similar and therefore for the sake of simplicity, the log-log linear regression model was used. The model was fit for each of the aortic root measures, and 95% prediction intervals were calculated.

To assess whether there were changes with age, longitudinal repeated-measures analyses were performed for each aortic root measurement and z -score as well as for hemoglobin and hematocrit. Specifically, a linear model with maximum likelihood estimation and either an unstructured variance-covariance form or heterogeneous compound symmetry form among the repeated measurements was fit for each outcome. Covariate adjustment was made for HIV status, age category, and HIV by age category for z -scores, and the actual aortic root measurements were also BSA-adjusted. The results were summarized with adjusted means and 95% confidence intervals (CI) by HIV status and age category. For group I, only measurements on children between 5 and 9 years of age were analyzed because of the limited number of measurements outside of this age range. Separate models were fit to adjust for stroke volume and hemoglobin.

For baseline analysis of association with aortic root z -scores, the first available serum HIV RNA level and CD4 cell count measurement within 3 months of the first echocardiogram was used. The Pearson product-moment correlation coefficient and the Spearman rank correlation coefficient were used to test for association between baseline covariates and between change in covariates. Change from baseline in z -scores was compared by means of the 1-sample t test. All statistical tests were 2-sided, and a P value $\leq .05$ was considered statistically significant.

Results

Patient demographics

Aortic root data were available on 280 study patients. Group I consisted of 86 children (of 205 group I children enrolled). Most of the children were black (50.0%) or Hispanic (29.1%), and 45.3% were male. Among the 194 group II infants with aortic root data available (of 600 enrolled), 50 were HIV-infected (group IIa) and 144 HIV-uninfected (group IIb). Within group II, 51.6% were black, 35.1% were Hispanic, and 53.1% were male. Normal aortic root data were obtained from 259 children (median age, 4.7 years); 57.9% were male. Of the 30% of the normal children on whom race was recorded, 24.4% were black, 15.3% were Hispanic, and 2.6% were Asian.

Treatment of HIV infection

Nearly every HIV-infected child enrolled in the P²C² HIV Study received antiretroviral treatment, principally zidovudine and dideoxyinosine, at some time during the study period (97.6% in group I and 91.4% in group IIa). Protease inhibitors were used by a small number of the study children (<5%). In addition, 43% of group I and 28% of the group IIa study patients were treated with intravenous immunoglobulin at some time during the study period.

Aortic root measurements

The relation between aortic root measurements and BSA for the 259 normal children is displayed in Figure 1. Diameter measurement of the aortic annulus was available on 257 children, of the sinuses of Valsalva on 207 children, and of the STJ on 160 children. The fitted regression equations are provided in the figure legend.

There were 672 echocardiograms performed on 280 study patients (232 echocardiograms in group I, 155 in group IIa, and 285 in group IIb). The median age at the time of first aortic root measurements was 48.7 months (72.9 in group I, 38.3 in group IIa, and 41.4 in group IIb), with a median number of 2.0 echocardiograms per patient (3.0 in group I, 3.0 in group IIa, and 2.0 in group IIb). Median duration of follow-up was 7.3 months for the study population (8.4 in group I, 10.7 in group IIa, and 6.0 in group IIb).

BSA-adjusted aortic root analyses are provided for group II in Figure 2. Aortic root size was significantly greater in HIV-infected children than in HIV-uninfected children. By repeated-measures analyses, mean aortic root measurements were significantly increased for HIV-infected children at 2 years of age (P value of .04, <.001, and .04 for aortic annulus diameter, sinuses of Valsalva, and STJ, respectively). Mean aortic root sizes were approximately 0.10 to 0.15 cm larger in HIV-infected children at 5 years of age (P value of .005, .002, and <.001 for aortic annulus diameter, sinuses of Valsalva, and STJ, respectively). As expected, the aortic root increased in size with increasing age and BSA (all P values <.01).

Model-based z -scores for aortic root measurements were more dilated in group IIa (HIV-infected) children than in group IIb (HIV-uninfected) children. At 30 months of age, the aortic annulus diameter z -scores were 1.03 (95% CI, 0.65 to 1.41) and 0.18 (95% CI, 0.00 to 0.39) for the HIV-infected and HIV-uninfected children, respectively. Mean z -scores for the sinuses of Valsalva and the STJ were also more dilated for the HIV-infected children (1.01, 95% CI, 0.74 to 1.28; 1.10, 95% CI, 0.65 to 1.54, respectively) compared with the HIV-uninfected children (0.65, 95% CI, 0.46 to 0.85; 0.83, 95% CI, 0.58 to 1.07, respectively). These differences did not increase over the course of follow-up.

BSA-adjusted aortic root analyses are provided for group I in Figure 3. Mean z -scores were significantly elevated by approximately 1.0 SD for each aortic root measurement relative to the external controls, a finding in agreement with results of the group II analyses. At 5 years of age, the mean z -scores were 1.06 (95% CI, 0.67 to 1.45), 1.19 (95% CI, 0.93 to 1.45), and 1.36 (95% CI, 0.97 to 1.74) for aortic annulus diameter, sinuses of Valsalva, and STJ, respectively. The mean z -scores did not become progressively higher over the course of follow-up.

The z -scores were +2 or higher for approximately 10% to 15% of the aortic root measurements among HIV-infected (groups I and IIa) children, and <5% of the z -scores were elevated among HIV-uninfected children (group IIb) (data not shown). The percent with elevated z -scores did not vary significantly with age.

Covariate analyses

Markers for vascular stress—Heart rate, systolic BP, and stroke volume were not significantly associated with aortic root size for group II. These covariates had only a small effect on the model-based means for aortic annulus diameter, sinuses of Valsalva, and STJ when comparing HIV-infected and HIV-uninfected children. The means for each aortic root measurement remained significantly elevated for group IIa children compared with group IIb children after adjusting for heart rate, systolic BP, and stroke volume.

Mean hemoglobin and hematocrit values over the first 5 years of life for group II children are provided in Figure 4. Both measures were consistently lower in the HIV-infected children. Therefore, aortic root analyses were adjusted with a single hemoglobin measurement for each child at 2 years of age. Hemoglobin was not significantly associated with aortic root measurements, although a trend toward correlation was seen at the level of the sinuses of Valsalva (*P* value of 0.18, 0.06, and 0.46 for aortic annulus diameter, sinuses of Valsalva, and STJ, respectively). Adjusting for hemoglobin did slightly reduce the magnitude of the mean difference for sinuses of Valsalva, but the differences remained significant at 24, 42, and 60 months of age.

Left ventricular end-diastolic dimension

The baseline correlation of aortic root measurements with LVEDD (first available pair) was tested for 45 group IIa children and 78 group I children. In the 45 group IIa children, mean LVEDD *z*-score was 0.29 ± 0.73 (mean \pm SD). There was a positive association between group IIa LVEDD and aortic root *z*-scores at the levels of the aortic annulus (0.96 ± 1.00 , Pearson coefficient of 0.43, *P* value of .003) and sinuses of Valsalva (0.86 ± 0.83 , Pearson coefficient of 0.31, *P* value of .04). In the 78 group I children, mean LVEDD *z*-score was 0.33 ± 0.90 . There was a positive association between group I LVEDD and aortic root *z*-scores at all levels: aortic annulus (1.03 ± 0.94 , Pearson coefficient of 0.44, *P* value $< .001$); sinuses of Valsalva (1.01 ± 0.83 , Pearson coefficient of 0.39, *P* value $< .001$); and STJ (1.06 ± 0.88 , Pearson coefficient of 0.38, *P* value of .001).

Data on change in aortic root measurements and change in LVEDD from the first available pair to the last were available for 42 group IIa children and 58 group I children. For group IIa children, median time between the first and last echocardiogram was about 8.5 months. The mean change in LVEDD was 0.1 cm and the mean change in aortic root measurements was 0.04, 0.07, and 0.05 cm for aortic annulus diameter, sinuses of Valsalva, and STJ, respectively. For group I children, median time between the first and last echocardiogram was approximately 10 months. The mean change in LVEDD was 0.1 cm and the mean change in aortic root measurements was 0.03, 0.06, and 0.04 cm for aortic annulus diameter, sinuses of Valsalva, and STJ, respectively. The mean change in *z*-scores did not differ from zero for any of the measurements. No correlation was detected between *z*-score changes in LVEDD and *z*-score changes in aortic root measurements.

Viral load and immune system dysfunction

Serum HIV RNA levels were available for 38 group IIa children and 68 group I children. A positive association was found between Log_{10} RNA and aortic root *z*-scores only for

measurements at the level of the sinuses of Valsalva. The relation was similar for both group IIa and group I children. For group IIa children, Log_{10} RNA was 4.26 ± 0.85 and sinuses of Valsalva mean z -score was 0.95 ± 0.95 (Pearson correlation coefficient of 0.32, P value of .05). For group I children, Log_{10} RNA was 4.20 ± 0.80 and sinuses of Valsalva mean z -score was 1.02 ± 0.88 (Pearson correlation coefficient of 0.34, P value of .006).

The association between CD4 cell count z -scores and aortic root measurements z -scores is provided in Tables I and II for group IIa children and group I children, respectively. There was a statistically significant negative association between the z -scores for each aortic root measurement and CD4 cell count for both HIV-infected cohorts.

Discussion

Mild and nonprogressive aortic root dilation was seen in children with vertically transmitted HIV infection from 2 to 9 years of age. Although a 0.1-cm difference in vessel diameter is relatively small, an increase in the diameter from 1.2 cm to 1.3 cm results in a 17% increase in vessel cross-sectional area, and an increase from 1.8 cm to 1.9 cm results in an 11% increase in cross-sectional area. Possible causes for aortic root dilation in HIV-infected patients include the following: (1) stress-modulated growth,^{7,8} (2) direct HIV infection of the aortic root, (3) systemic or focal coinfection, (4) associated treatment of HIV infection, (5) immune complex-mediated involvement of the aortic root, (6) cytokine- or lymphokine-mediated alteration of the aortic root,^{9,10} or (7) central immune dysregulation (list modified from Calabrese et al¹¹).

Stress-modulated growth

This study primarily addressed the possibility of stress-modulated aortic root growth, with heart rate, systolic BP, stroke volume, hemoglobin, and hematocrit used as surrogate markers for vascular stress. None of these markers was associated with aortic root dilation in the group II children.

In both HIV-infected study cohorts (groups I and IIa), a positive association was found between LVEDD and aortic root z -scores at baseline. There was no correlation between z -score changes in LVEDD and z -score changes in aortic root measurements. We have previously reported nonprogressive left ventricular dilation as one of the abnormalities of left ventricular structure and function among 196 group I children.¹² In children with sickle-cell anemia, increased left ventricular and aortic root dimensions have been reported to correlate well with hemoglobin level.¹³ In the current study, although dilation of both the left ventricle and aortic root were seen in the HIV-infected study cohorts, aortic root dimensions did not correlate with stroke volume and only trended toward correlation with hemoglobin level at the level of the sinuses of Valsalva. Thus a direct effect of HIV infection on left ventricular and aortic root dimensions cannot be excluded.

Direct HIV infection

Higher serum HIV RNA levels were associated with dilation of the aortic root at the level of the sinuses of Valsalva at baseline in both HIV-infected study cohorts. A high viral load has been associated with rapid disease progression in infants with vertically transmitted HIV

infection.⁵ Evidence of injury, regeneration, and activation of the aortic endothelium in HIV-infected patients has been shown by Zeitz et al.¹⁴ They postulated that abnormal endothelial function might contribute to the pathogenesis and progression of AIDS (for example, abnormal vascular permeability in HIV-associated encephalopathy and abnormal endothelial regulation of immune system function); plus, it might be relevant to microvascular proliferation and the initiation of Kaposi sarcoma. It is possible that endothelial damage may also involve factors that modulate aortic growth. Ascherl et al⁹ have shown that vascular endothelial growth factor- A secretion by T-lymphocytes was promoted by inflammatory cytokines in conditioned medium derived from HIV-infected T-lymphocytes.

Immune system dysfunction

Aortic root dilation may be present in certain disorders associated with an inflammatory response, such as ankylosing spondylitis,¹⁵ and Takayasu arteritis.¹⁶ Potentially immune-mediated arteriopathies are also seen in Kawasaki disease¹⁷ and cardiac allograft atherosclerosis.¹⁸ The mechanisms of immune-related vascular involvement in these abnormalities are not well understood, and the list of potential causes is similar to that provided above for aortic root dilation in HIV-infected patients.

Studies with transgenic models of HIV infection have demonstrated vasculopathy in the absence of HIV replication. Tinkle et al¹⁹ showed extensive vasculopathy in transgenic mice carrying a replication-defective HIV-1 provirus. The inflammatory response occurred primarily in the adventitial layer without involvement of the endothelium.

Aneurysmal lesions in HIV infection

In a recent review of vascular lesions associated with HIV infection, Starc and Joshi²⁰ included 35 aneurysmal lesions of small and large arteries in patients ranging from 3 to 64 years of age. In most reported instances, aneurysms of the aorta in HIV-infected patients were associated with secondary or opportunistic infections. There is one report in the literature of a “true” aneurysm of the ascending aorta in a 31-year-old HIV-infected man with a history of intravenous drug abuse²¹ and another case of a ruptured aneurysm of the sinus of Valsalva in a 27-year-old HIV-infected woman.³

A lymphoproliferative inflammatory response has been associated with aneurysmal lesions in patients with HIV infection, but involvement of the aorta has only infrequently been described.^{11,22} In a report of atypical arterial aneurysms in 16 young adult patients (12 HIV-infected), Marks and Kuskov²² presented 5 cases associated with fibroproliferative vascular disease. Granulomatous periarteritis was seen in the abdominal aorta below the origin of the superior mesenteric artery in 2 patients and in the common and external iliac arteries in 3 patients.

Nair et al² recently described 28 HIV-infected patients (median age, 30 years) with 92 arterial aneurysms, including 5 aneurysms of the thoracoabdominal aorta and 7 of the abdominal aorta. Aortic aneurysms were usually seen in association with other aneurysms. In a related report, a predominantly aneurysmal vasculopathy was seen in the large arteries of 16 HIV-infected young adults.²³ Important pathologic features included leukocytoclastic

vasculitis of vasa vasora and periadventitial vessels. In these two reports, an underlying cause of the HIV-associated aneurysms was not identified.

Limitations

Routine aortic root measurements were not available during the first 2 years of life, and the study did not determine the onset of aortic root dilation in HIV-infected versus HIV-uninfected children. Aortic root dilation appeared to be nonprogressive, but long-term follow-up was not available. Whereas aortic root dilation in HIV-infected children did not appear to be strongly associated with markers of increased vascular stress, the mechanism of HIV-associated aortic root dilation was not further elucidated. The confounding effect of HIV treatment on aortic root size could not be assessed because nearly every HIV-infected child received antiretroviral medications at some time during the study period.

Conclusions

Mild and nonprogressive aortic root dilation was seen in children with vertically transmitted HIV infection from 2 to 9 years of age. Aortic root size was not significantly associated with markers for stress-modulated growth; however, aortic root dilation was associated with left ventricular dilation, an increased viral load, and a lower CD4 cell count in HIV-infected children at baseline. Although the degree of aortic root dilation remained stable during the study period, the natural history of HIV-associated aortic root dilation is unknown. As prolonged survival of HIV-infected patients becomes more prevalent, some patients may require long-term follow-up of aortic root size.

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References

1. Joshi VV, Pawel B, Connor E, et al. Arteriopathy in children with acquired immune deficiency syndrome. *Pediatr Pathol.* 1987; 7:261–275. [PubMed: 3684808]
2. Nair R, Robbs JV, Naidoo NG, et al. Clinical profile of HIV-related aneurysms. *Eur J Vasc Endovasc Surg.* 2000; 20:235–240. [PubMed: 10986021]
3. Bhagat K, Mombeshora S, Naik K, et al. Images in cardiovascular medicine: ruptured aneurysm of the sinus of Valsalva. *Cent Afr J Med.* 1999; 45:184–186. [PubMed: 10695197]
4. P²C² HIV Study Group. The pediatric pulmonary and cardiovascular complications of vertically transmitted human immunodeficiency virus (P²C² HIV) infection study: design and methods. *J Clin Epidemiol.* 1996; 49:1285–1294. [PubMed: 8892497]
5. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1: Women and Infants Transmission Study Group. *N Engl J Med.* 1997; 336:1337–1342. [PubMed: 9134873]
6. Mofenson LM, Bethel J, Moye J Jr, et al. Effect of intravenous immunoglobulin (IVIG) on CD4+ lymphocyte decline in HIV-infected children in a clinical trial of IVIG infection prophylaxis: the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *J Acquir Immune Defic Syndr.* 1993; 6:1103–1113. [PubMed: 8105072]

7. Taber LA, Eggers DW. Theoretical study of stress-modulated growth in the aorta. *J Theor Biol.* 1996; 180:343–357. [PubMed: 8776466]
8. Jones EC, Devereux RB, O'Grady MJ, et al. Relation of hemodynamic volume load to arterial and cardiac size. *J Am Coll Cardiol.* 1997; 29:1303–1310. [PubMed: 9137228]
9. Ascherl G, Hohenadl C, Schatz O, et al. Infection with human immunodeficiency virus-1 increases expression of vascular endothelial cell growth factor in T cells: implications for acquired immunodeficiency syndrome-associated vasculopathy. *Blood.* 1999; 93:4231–4241.
10. Conaldi PG, Serra C, Dolei A, et al. Productive HIV-1 infection of human vascular endothelial cells requires cell proliferation and is stimulated by combined treatment with interleukin-1 beta plus tumor necrosis factor-alpha. *J Med Virol.* 1995; 47:355–363. [PubMed: 8636703]
11. Calabrese LH, Estes M, Yen-Lieberman B, et al. Systemic vasculitis in association with human immunodeficiency virus infection. *Arthritis Rheum.* 1989; 32:569–576. [PubMed: 2655605]
12. Lipshultz SE, Easley KA, Orav J, et al. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P²C² HIV multicenter study. *Circulation.* 1998; 97:1246–1256. [PubMed: 9570194]
13. Lester LA, Sodt PC, Hutcheon N, et al. Cardiac abnormalities in children with sickle cell anemia. *Chest.* 1990; 98:1169–1174. [PubMed: 2146092]
14. Zeitz C, Hotz B, Sturzl M, et al. Aortic endothelium in HIV-1 infection. *Am J Pathol.* 1996; 149:1887–1898. [PubMed: 8952525]
15. LaBresh KA, Lally EV, Sharma SC, et al. Two-dimensional echocardiographic detection of preclinical aortic root abnormalities in rheumatoid variant diseases. *Am J Med.* 1985; 78:908–912. [PubMed: 4014267]
16. Brantley BD, Forman MB, Virmani R. Diagnosis and treatment of Takayasu's arteritis. *Prim Cardiol.* 1990; 16:47–51. 54.
17. Leung DY. The potential role of cytokine-mediated vascular endothelial activation in the pathogenesis of Kawasaki disease. *Acta Paediatr Jpn.* 1991; 33:739–744. [PubMed: 1801553]
18. Grattan MT, Moreno-Cabral CE, Starnes VA, et al. Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *JAMA.* 1989; 261:3561–3566. [PubMed: 2542633]
19. Tinkle BT, Ngo L, Luciw PA, et al. Human immunodeficiency virus-associated vasculopathy in transgenic mice. *J Virol.* 1997; 71:4809–4814. [PubMed: 9151876]
20. Starc, TJ.; Joshi, VV. Vascular disease in HIV infection. In: Lipshultz, SE., editor. *Cardiology in AIDS.* New York: Chapman & Hall; 1998. p. 209-222.
21. Boggian K, Leu HJ, Schneider J, et al. True aneurysm of the ascending aorta in HIV disease [in German]. *Schweiz Med Wochenschr.* 1994; 124:2083–2087. [PubMed: 7973546]
22. Marks C, Kuskov S. Pattern of arterial aneurysms in acquired immunodeficiency disease. *World J Surg.* 1995; 19:127–132. [PubMed: 7740798]
23. Chetty R, Batitang S, Nair R. Large artery vasculopathy in HIV-positive patients: another vasculitic enigma. *Hum Pathol.* 2000; 31:374–379. [PubMed: 10746682]

Appendix

A partial list of participants in the P²C² HIV study is listed below, with Principal Investigators identified with an asterisk. A complete list of study participants can be found in Reference 4.

National Heart, Lung, and Blood Institute:

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Beth Israel Medical Center: Mary Anne Worth, RN.

Presbyterian Hospital in the City of New York/Columbia University, New York, NY: Robert Mellins, MD,* Fred Bierman, MD* (through 5/91), Thomas Starc, MD, MPH, Anthony Brown, Margaret Challenger, and Kimberly Geromanos, RN, MS, CNS.

UCLA School of Medicine, Los Angeles, Calif: Samuel Kaplan, MD,* Y. Al-Khatib, MD, Robin Doroshov, MD, Josephine Isabel-Jones, MD, Roberta Williams, MD, Helene Cohen, RN, PNP, Sharon Golden, RDMS, Karen Simandle, RDMS, and Ah-Lin Wong, RDMS.

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Policy, data, and safety monitoring board:

Henrique Rigatto, MD, (Chairman), Edward B. Clark, MD, Robert B. Cotton, MD, Vijay V. Joshi, MD, Paul S. Levy, ScD, Norman S. Talner, MD; Patricia Taylor, PhD, Robert Tepper, MD, PhD, Janet Wittes, PhD, Robert H. Yolken, MD, and Peter E. Vink, MD.

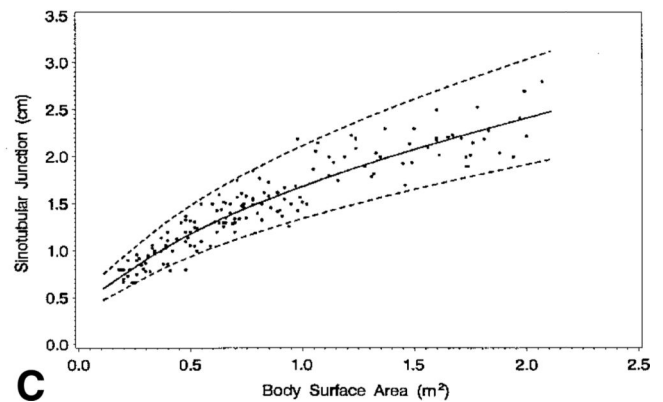
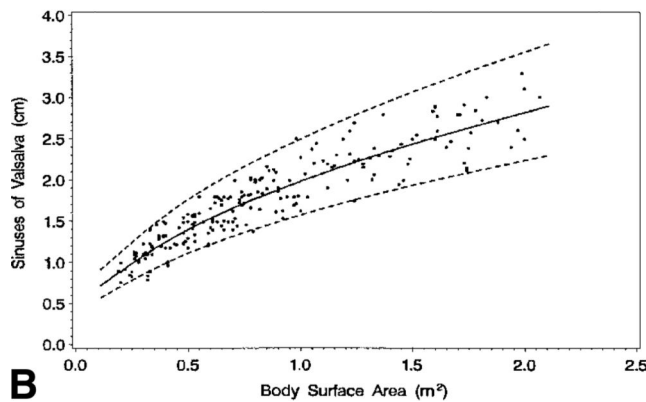
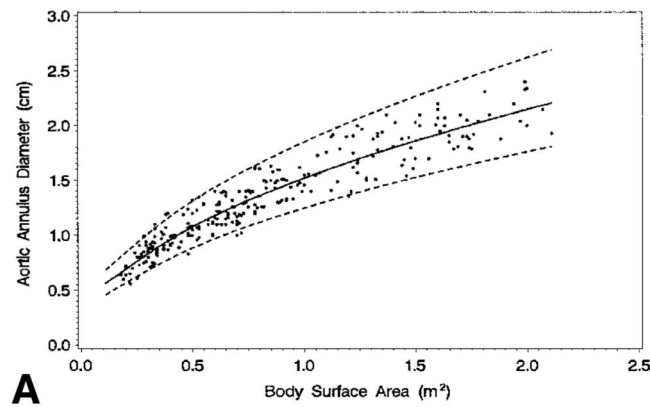


Figure 1.

BSA-adjusted increase in aortic root measurements for 259 control children (median age, 4.7 years). **A**, Linear regression of log aortic annulus diameter (cm) on log body surface area (m^2). Aortic annulus diameter = $0.419 + 0.498 \text{ Log (BSA)}$, $SD = 0.100$. **B**, Linear regression of log sinuses of Valsalva (cm) on log body surface area (m^2). Sinuses of Valsalva = $0.688 + 0.504 \text{ log (BSA)}$, $SD = 0.116$. **C**, Linear regression of log STJ (cm) on log body surface area (m^2). $STJ = 0.522 + 0.517 \text{ log (BSA)}$, $SD = 0.115$. Solid lines are back-transformed, fitted regression equations; dashed lines are 95% prediction limits.

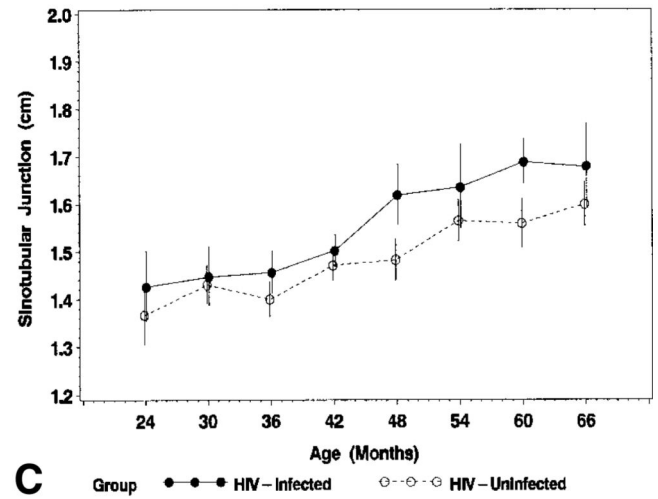
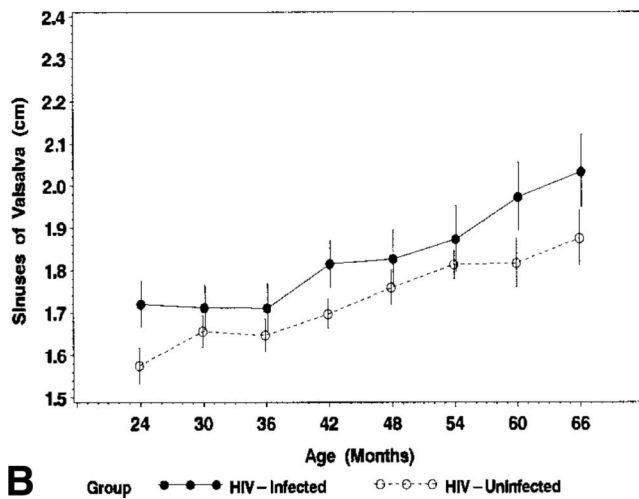
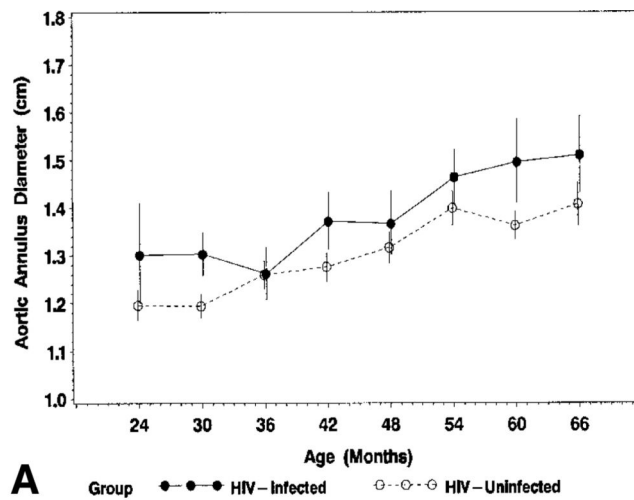


Figure 2. Model-based means and 95% CI for BSA-adjusted aortic root measurements by age according to HIV status among group II children. **A**, Aortic annulus diameter, cm (49 HIV-infected children and 144 HIV-uninfected children); **B**, sinuses of Valsalva, cm (48 HIV-infected children and 142 HIV-uninfected children); and **C**, STJ (cm) (48 HIV-infected children and 139 HIV-uninfected children).

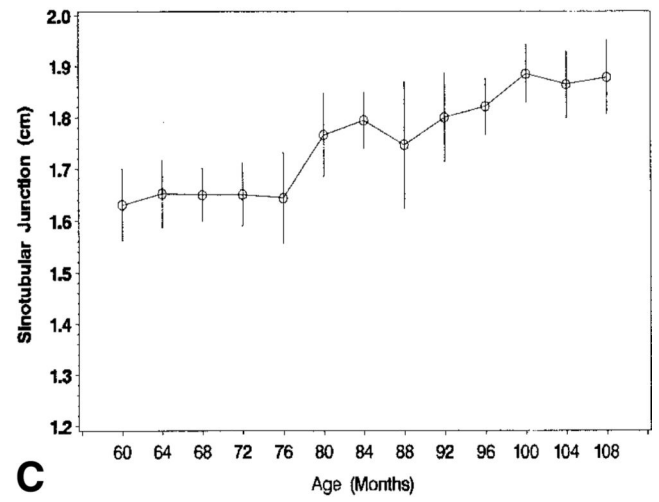
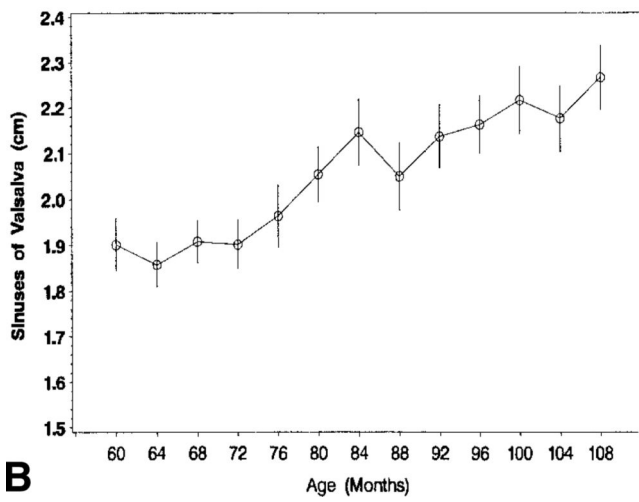
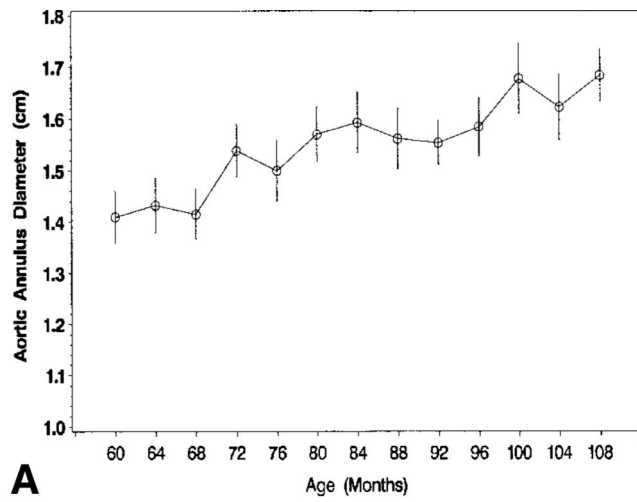


Figure 3. Model-based means and 95% CI for BSA-adjusted aortic root measurements by age for group I children. **A**, Aortic annulus diameter (cm) (86 HIV-infected children); **B**, sinuses of Valsalva (cm) (84 HIV-infected children); **C**, STJ (cm) (80 HIV-infected children).

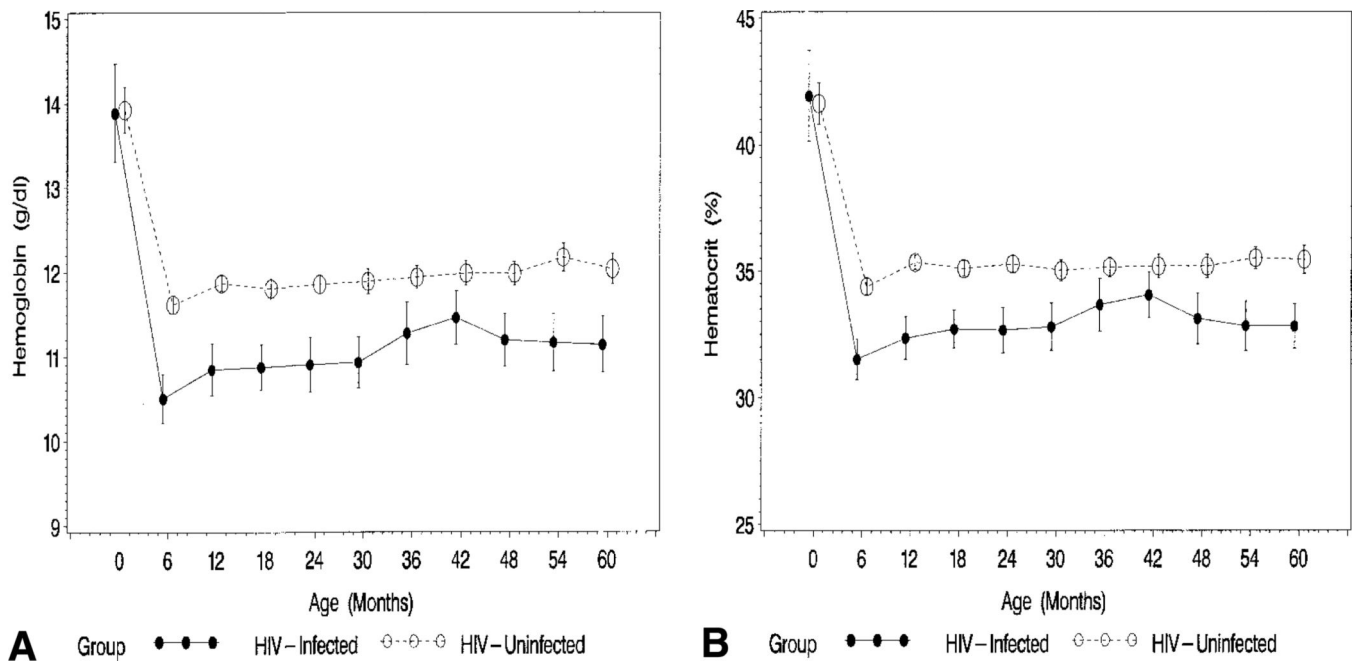


Figure 4.

Model-based means and 95% CI for hemoglobin and hematocrit by age according to HIV status among group II children. **A**, Hemoglobin (g/dL) (93 HIV-infected children and 462 HIV-uninfected children); **B**, hematocrit (%) (93 HIV-infected children and 462 HIV-uninfected children).

Correlation of first pair of aortic root measurements with CD4 cell count z-score for HIV-infected neonatal cohort

Table 1

Variable	Descriptive statistics							Correlation with CD4 z-score			
	n	Mean	SD	Median	Min	Max	r	r*	P value	r _s	P value
CD4 z-score	49	-1.65	0.80	-1.82	-3.01	0.65	—	—	—	—	—
Aortic annulus diameter z-score	49	0.90	1.13	1.05	-2.22	2.86	-0.30	0.04	-0.42	.002	.002
Aortic annulus diameter (cm)	49	1.33	0.17	1.30	0.97	1.71	-0.24	.10	-0.29	.04	.04
Age (mo)	49	39.8	12.4	36.7	19.3	61.4	—	—	—	—	—
CD4 z-score	48	-1.70	0.74	-1.84	-3.01	0.37	—	—	—	—	—
Sinuses of Valsalva z-score	48	0.98	0.95	0.94	-1.43	2.92	-0.42	.003	-0.49	<.001	<.001
Sinuses of Valsalva (cm)	48	1.78	0.21	1.76	1.40	2.33	-0.37	.01	-0.39	.006	.006
Age (mo)	48	39.6	12.5	36.5	19.3	61.4	—	—	—	—	—
CD4 z-score	49	-1.72	0.72	-1.82	-3.01	0.37	—	—	—	—	—
STJ z-score	49	1.15	1.08	1.15	-1.46	3.61	-0.52	<.001	-0.60	<.001	<.001
STJ (cm)	49	1.54	0.23	1.49	1.17	2.19	-0.39	.006	-0.43	.002	.002
Age (mo)	49	40.3	12.4	36.7	19.3	61.4	—	—	—	—	—

* r indicates Pearson product-moment correlation coefficient; r_s, Spearman rank correlation coefficient.

Correlation of first pair of aortic root measurements with CD4 cell count z-score for older HIV-infected cohort

Table II

Variable	Descriptive statistics							Correlation with CD4 z-score		
	n	Mean	SD	Median	Min	Max	r*	P value	r _s *	P value
CD4 z-score	100	-2.31	0.87	-2.40	-3.60	0.15	—	—	—	—
Aortic annulus diameter z-score	101	1.07	1.05	1.13	-2.83	3.47	-0.31	.002	-0.32	.001
Aortic annulus diameter (cm)	101	1.55	0.21	1.56	0.98	1.99	-0.15	.13	-0.19	.06
Age (mo)	101	84.9	28.5	77.1	39.4	193.9	—	—	—	—
CD4 z-score	97	-2.32	0.87	-2.44	-3.60	0.15	—	—	—	—
Sinuses of Valsalva z-score	98	1.03	0.86	0.99	-0.72	3.42	-0.28	.006	-0.31	.002
Sinuses of Valsalva (cm)	98	2.05	0.27	2.00	1.55	2.75	-0.15	.15	-0.17	<.001
Age (mo)	98	85.5	28.7	78.1	39.4	198.9	—	—	—	—
CD4 z-score	90	-2.35	0.85	-2.51	-3.60	-0.15	—	—	—	—
STJ z-score	91	1.13	0.97	1.13	-2.58	3.37	-0.20	.06	-0.24	.02
STJ (cm)	91	1.76	0.24	1.76	1.10	2.36	-0.08	.43	-0.13	.21
Age (mo)	91	86.9	28.7	80.3	39.4	193.9	—	—	—	—

* r indicates Pearson product-moment correlation coefficient; r_s, Spearman rank correlation coefficient.