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Left Ventricular Structure and Function in Children Infected With Human Immunodeficiency Virus:
The Prospective P²C² HIV Multicenter Study

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Abstract

Background—The frequency of, course of, and factors associated with cardiovascular abnormalities in pediatric HIV are incompletely understood.

Methods and Results—A baseline echocardiogram (median age, 2.1 years) and 2 years of follow-up every 4 months were obtained as part of a prospective study on 196 vertically HIV-infected children. Age- or body surface area–adjusted z scores were calculated by use of data from normal control subjects. Although 88% had symptomatic HIV infection, only 2 had CHF at enrollment, with a 2-year cumulative incidence of 4.7% (95% CI, 1.5% to 7.9%). All mean cardiac measurements were abnormal at baseline (decreased left ventricular fractional shortening [LV FS] and contractility and increased heart rate and LV dimension, mass, and wall stresses). Most of the abnormal baseline cardiac measurements correlated with depressed CD4 cell count z scores and the presence of HIV encephalopathy. Heart rate and LV mass showed significantly progressive abnormalities, whereas FS and contractility tended to decline. No association was seen between

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The institutions and investigators participating in this study are listed in the Appendix.
longitudinal changes in FS and CD4 cell count z score. Children who developed encephalopathy during follow-up had depressed initial FS, and FS continued to decline during follow-up.

**Conclusions**—Subclinical cardiac abnormalities in HIV-infected children are common, persistent, and often progressive. Dilated cardiomyopathy (depressed contractility and dilatation) and inappropriate LV hypertrophy (elevated LV mass in the setting of decreased height and weight) were noted. Depressed LV function correlated with immune dysfunction at baseline but not longitudinally, suggesting that the CD4 cell count may not be a useful surrogate marker of HIV-associated LV dysfunction. However, the development of encephalopathy may signal a decline in FS.

**Keywords**

HIV; AIDS; pediatrics; heart failure; cardiomyopathy

Several patterns of cardiovascular involvement have been reported in HIV-infected children.\(^1\)–\(^12\) A continuum from asymptomatic LV dysfunction to dilated cardiomyopathy to CHF to hypotensive pump failure with cardiac-associated mortality has been suggested.\(^13\) Abnormalities of LV hypertrophy have also been suggested in which LV mass is excessive for BSA but insufficient for LV dimension, resulting in a sustained elevation of LV peak wall stress, a mediator of mechanically induced hypertrophy.\(^2,14,15\) Other reported cardiac problems include hemodynamic abnormalities, conduction abnormalities, dysrhythmias, and sudden death, as well as pericardial and vascular involvement.\(^1\)–\(^12\) The causes of these abnormalities are likely to be multifactorial.\(^8,13\)

LV dysfunction and cardiomyopathy have been identified in HIV-infected children. Dilated cardiomyopathy appears to be more common in HIV-infected children than in seroreverted children and increases in frequency as HIV-infected children progress to AIDS.\(^2,12\) CHF appears to occur chronically in \(\approx 10\%\) of HIV-infected children and transiently in another 10%.\(^4\) Cardiomyopathy appears to reduce survival in HIV-infected children.\(^3,5,6,9,16\) One study found a relative risk of death of 2.76 in children with cardiomyopathy compared with children without cardiomyopathy.\(^3\) Children were more likely to be short-term survivors (<5 years) if cardiomyopathy was present.\(^7\) In one center, 25% of HIV-infected children who died had cardiomyopathy or died suddenly; 83% of these children had premorbid cardiomyopathy or arrhythmias.\(^6\)

Risk factors for more advanced cardiac involvement in HIV-infected children have been suggested\(^4\) and may be useful for monitoring or identification for interventions. These risk factors include HIV encephalopathy\(^4,17\) and a low CD4 cell count.\(^9,10,18\) There are conflicting reports on the use of CD4 cell count as a surrogate marker for HIV-associated heart disease.\(^11,13\)

Previous studies describing cardiac involvement in HIV-infected children were not specifically designed to evaluate serial LV function and have limitations that make it difficult to understand accurately the extent of cardiac involvement. These limitations include a lack of uniform cardiac definitions or monitoring, retrospective study design, use of cross-sectional echocardiographic data, focus on a single echocardiographic parameter,
small number of patients, and bias in selection of patients. We therefore conducted a prospective longitudinal study to monitor heart disease and the progression of cardiac abnormalities in asymptomatic and symptomatic HIV-infected children. We performed multiple cardiac measurements with central remeasurements in a consecutive series of geographically diverse children with primarily symptomatic HIV infection with testing at defined time points to more clearly elucidate cardiac involvement in HIV-infected children. We hypothesized that HIV-infected children would develop dilated cardiomyopathy, as assessed by measurements of LV function (FS), contractility (stress-velocity index), afterload (end-systolic wall stress), and size (end-diastolic dimension); abnormal LV hypertrophy, as assessed by measurements of LV mass and the adequacy of hypertrophy (peak-systolic wall stress); and hemodynamic abnormalities, as assessed by measurements of heart rate and blood pressure. The baseline and first 2 years of longitudinal echocardiographic data are presented, as well as correlation of LV structure and function with CD4 cell count and encephalopathy.

**Methods**

Two hundred five children >28 days old with documented vertically transmitted HIV infection were enrolled between May 1990 and April 1993. All children were born after April 1, 1985, except when vertical transmission of HIV infection could be documented with reasonable medical certainty. HIV infection was considered to be vertically transmitted if the mother was HIV infected or had died of AIDS and there was no history of sexual abuse of the child before enrollment. Children with cancer at enrollment were excluded. The patients underwent serial echocardiographic evaluations as part of a natural history study of cardiac and pulmonary complications of vertically transmitted HIV infection at five clinical centers located in distinct areas of the United States, as detailed by Kattan et al. All studies followed a protocol approved by the institutional review board at each clinical center. Informed consent was obtained from patients or their families. Patient history was obtained prospectively during visits of the patients to the clinic or by review of medical records.

We classified each patient’s HIV disease status at the time of echocardiography according to the 1987 pediatric HIV disease classification system of the CDC. The blood T-cell lymphocyte subpopulation of CD4 cells was counted in laboratories that used AIDS Clinical Trials Group quality assurance protocols, and z scores for age-adjusted CD4 cell counts were determined.

We defined CHF as the presence of clinical signs and symptoms of heart failure, as determined by a pediatric cardiologist, treated with anticongestive therapy.

All children underwent echocardiographic testing because of study protocol requirements at predetermined intervals and not specifically for evaluation of cardiac disease. To ensure uniformity of echocardiographic measurements, all echocardiograms were remeasured at one central location by one of two technicians unaware of the clinical status or medications of the patient. Site visits were performed early in the study, and regular feedback was given after central remeasurement to ensure uniform techniques for the performance of echocardiograms. Before each echocardiographic study, children <4 years old were sedated.
as necessary. Two-dimensional echocardiography and Doppler studies with stress-velocity analysis were performed in each child. We measured systolic and diastolic blood pressure using a Dinamap automated vital-signs monitor (Critikon, Inc). The combined M-mode echocardiogram, phonocardiogram, pulse tracing, ECG, and blood pressure reading were analyzed with a computer program. We determined LV contractility from the relation between end-systolic LV wall stress and the rate-adjusted velocity of fiber shortening, a previously validated index of contractility that incorporates afterload and is independent of preload. Contractility was defined as the standardized difference between the observed and the expected values of the rate-adjusted velocity of fiber shortening. Afterload was measured as meridional end-systolic LV wall stress. Peak systolic wall stress is a determinant of hypertrophy, not function, and was measured as previously defined. LV mass (in grams) was calculated from the M-mode measurements by the method of Devereux et al.

Normative values for each of the echocardiographic measures by age or BSA were developed by use of data from 285 normal children measured at the same central digitizing facility in the same manner as the study patient data. The regression lines with 95% prediction intervals for the normal children are shown in Fig 1A through 1F. Age- or BSA-adjusted z scores were created for the HIV-infected children to adjust for the changes in LV size and structure associated with growth by taking each echocardiographic measure, subtracting the age- or BSA-appropriate mean, and dividing by 1 SD. Therefore, a z score of 0 represents a measurement that equals the normal mean value for the child’s age or BSA, whereas a z score of −2 represents a measurement 2 SD below average for age or BSA. Age correction was used for FS, wall stresses, blood pressure, and heart rate; BSA correction was used for LV dimension and mass. The regression equations for cardiac structure and function measures developed from 285 normal infants and children for this study are listed in Appendix 1. Details on the data from normal children and the nonlinear models can be found in Colan et al.

Dilated cardiomyopathy is defined as a child having both LV contractility >2 SD below the normal mean and LV end-diastolic dimension >2 SD above the normal mean. Inadequate LV hypertrophy is defined as a reduced ratio of LV thickness to LV dimension and elevated peak systolic wall stress. Inappropriate LV hypertrophy is defined as elevated LV mass for BSA in the setting of decreased height and weight for age and sex.

Statistical Analyses

**Baseline Data**—Mean z scores for each cardiac measurement were compared with a score of zero by a one-sample t test. The Spearman rank correlation coefficient was used to determine the association between baseline echocardiographic parameters and CD4 cell count z scores. ANCOVA was used to compare cardiac function measures by baseline HIV encephalopathy status.

**Longitudinal Data**—To assess whether there were changes over time, a longitudinal repeated-measures analysis was performed for each cardiac function measurement and z score. Specifically, a linear model using maximumlikelihood estimation and an unstructured
variance-covariance form among repeated measurements was fitted for each cardiac outcome. Covariate adjustment was made for time on study, age, age by time on study, digitizing technician, and baseline CD4 cell count z score. The results were summarized with adjusted means and 95% CIs for all children when the statistical interaction between age and time on study was not significant and by age category when the interaction between age and time on study was significant. The exception was LV mass, for which the interaction term was not significant but age was significant. Therefore, we report both the adjusted means for all children and also the adjusted means by age category.

Longitudinal Correlations—The rate of decline in cardiac function measures was determined by a random-coefficients model, in which the regression of z score on time since the initial echocardiogram was assumed to be linear, allowing a random intercept and slope for each child. To estimate the correlation between the rates of decline in FS and CD4 cell count z scores, a bivariate linear random-effects model was fitted, allowing estimation of the correlation between the true underlying intercepts and slopes for CD4 cell count and FS z scores.24

Results

Of the 205 children enrolled, 196 had a centrally remeasured echocardiographic evaluation available for this analysis. Nine children were not included in the analysis because of the inability to digitize the initial echocardiogram for 5 children and absence of an echocardiogram for 4 other children lost to follow-up. The initial echocardiogram was performed within 3 months of enrollment for 71% of participants (n=139). The age at initial echocardiography was <1 year in 23.5% (n=46), 1 to 2 years in 23.0% (n=45), 2 to 4 years in 23.5% (n=46), and ≥4 years in 30.1% (n=59).

The baseline descriptive statistics for the 196 children with echocardiographic data are shown in Table 1. The study population largely had symptomatic HIV infection with immunosuppression and reduced height and weight at 2.1 years old (median). The mean CD4 cell z score of −1.86 shown in Table 1 is also significantly less than normal (P<.001). Sixty-three percent of the children received zidovudine treatment at enrollment. Two children had CHF at initial cardiac evaluation, and 8 developed CHF during the 2 years of follow-up. The 2-year cumulative incidence of CHF was 4.7% (95% CI, 1.5% to 7.9%), excluding the 2 presenting cases. Thirty-two children died during the 2-year study period.

The mean values of all echocardiographic parameters were significantly abnormal at enrollment (Table 2). There was a pattern of decreased overall LV performance, with the mean FS z score nearly 1 SD below normal and the raw mean FS almost 2.5% below normal (expected mean of 37.0% versus observed mean of 34.6%). For 31% (60/196) of patients, the LV FS z score was more than 2 SD below normal. This decrease appeared to be the result of both depressed contractility and increased afterload as measured by end-systolic wall stress. The high end-systolic stress was the result of reduced LV posterior wall thickness (mean z score, −0.31; SD, 1.4; P=.003) as well as increased end-systolic blood pressure (Table 1) and LV dimension (Table 2). LV dimension was elevated with reduced wall thickness, resulting in a reduced thickness-to-dimension ratio (mean z score, −0.42; SD,
1.4; \( P < .001 \)), even though LV mass was increased above the normal mean for BSA.

Increased heart rate and diastolic blood pressure (mean \( z \) score, 0.49; SD, 1.1; \( P < .001 \)) were noted at the time of baseline echocardiography. Baseline echocardiographic parameters in comparison with normative values are shown for individual children in Fig 1, and raw and expected means are given in Table 2.

Table 3 demonstrates the association of baseline echocardiographic parameters with CD4 cell count \( z \) score and HIV encephalopathy status. We found significant correlations between CD4 cell count and all echocardiographic measurements except LV peak wall stress. Children with the most depressed FS or dilated end-diastolic dimension had the lowest CD4 cell counts.

At baseline, 40 children (20.4%) were classified as having neurological disease (CDC class P2B). An additional 22 children (11.2%) developed progressive neurological disease during the 2 years of follow-up. The remaining 134 children (68.4%) never developed progressive neurological disease. The relations between cardiac and neurological involvement were significant; children with encephalopathy had depressed FS and elevated end-systolic wall stress and heart rate (Table 3).

Table 4 lists the time trends for the echocardiographic parameters from Table 3. There is a decline in FS \( z \) score from −0.9 SD at 1 to 3 months on study to −1.32 SD at 22 to 26 months on study, which approaches statistical significance (\( P = .06 \) for linear trend) in the covariateadjusted model including adjustment for the significant effect of the echocardiographic digitizer (\( P = .004 \)). Note, however, in Table 4 that much of the decline in FS occurs during the first 3 months. Subgroup analyses show a significant decline in FS of −0.30 SD per year among the 164 children who did not die within 2 years (intercept±SE=−0.8±0.14, slope±SE=−0.30±0.08). In addition, children with an initial FS \( z \) score >0 had a significant decline of 0.79 SD per year (\( P < .001 \); intercept±SE=0.66±0.14, slope±SE=−0.79±0.12). However, those with an initial FS \( z \) score between −2 and 0 or a severely depressed initial FS \( z \) score ≤−2 did not change over time.

Similarly, Table 4 shows that heart rate increases from 1.01 SD above normal at 1 to 3 months on study to 1.52 SD above normal at 22 to 26 months on study (\( P = .001 \)). LV end-diastolic dimension \( z \) score was not found to change significantly (\( P = .23 \)). There was a significant increase in LV mass \( z \) score with increasing time on the study (\( P = .02 \)) and age (\( P = .006 \)). The other cardiac parameters were found to change with time according to enrollment age. The patterns of change are detailed in Table 5 and Fig 2. The overall trends were for increases in LV mass and in end-systolic and peak-systolic wall stresses and for depression of contractility over time. Even though each age subgroup has a small number of patients, several significant results were noted from the longitudinal repeated-measures analysis (\( P < .0125 \) with a Bonferroni adjustment for multiple comparisons). The mean LV end- and peak-systolic wall stress \( z \) scores significantly increased over time for children who enrolled at ≥4 years old (\( P < .001 \) for linear trend over time for each). This is consistent with the data in Table 2 and the finding that decreased FS is due to both depressed contractility and elevated afterload. Similarly, LV contractility decreased with time for older children (≥4 years old at enrollment) and for children <1 year old at enrollment. However, for children
who enrolled at 2 to 3 years old, the mean LV contractility did not change and the mean increased for children 1 to 2 years old at enrollment. These different trends in mean LV contractility support the observed interaction between age groups and time on study ($P=0.03$).

Table 6 shows the results of fitting a longitudinal model relating FS and CD4 cell counts for those 137 children with two or more paired measurements who did not die during the 2 years of follow-up. The table indicates that FS starts at 0.61 SD below normal and declines significantly by 0.46 SD per year.

Similarly, in Table 6, CD4 cell counts are initially 1.68 SD below normal and decline by 0.22 SD per year. The decline in FS shows a small and nonsignificant correlation with the decline in CD4 cell counts ($r=0.14; P=0.56$). In contrast, the initial CD4 cell counts and FS $z$ scores are correlated significantly ($r=0.3; P=0.02$). Note, however, that CIs for these estimates are wide, and the results may change as data from later follow-up observations are included.

Table 7 shows that the children who developed encephalopathy during follow-up had both depressed FS at baseline ($z$ score, $−0.9$ SD) and a decline during follow-up ($−0.95$ SD per year, $P<0.001$; 95% CI, $−0.44$ to $−1.46$). In contrast, the children who had encephalopathy at baseline and throughout follow-up had depressed FS initially ($z$ score, $−0.93$) but showed only a mild decline during follow-up ($−0.33$ SD per year; $P=0.26$), whereas the children who had never had encephalopathy had mildly depressed FS at baseline ($z$ score, $−0.5$) and showed only a moderate decline ($−0.42$ SD per year; $P<0.001$). These results suggest that despite a depressed baseline FS, children in whom encephalopathy developed will have a marked further decline in FS. In contrast, the yearly decline in CD4 cell counts was roughly equivalent regardless of whether encephalopathy was present or developed during follow-up. These results are based on sparse data and may be revised with further follow-up. There is no statistical difference between the slopes or the adjusted means for FS or CD4 cell count $z$ scores according to the presence, absence, or development of encephalopathy.

**Discussion**

Subclinical cardiovascular abnormalities are common in HIV-infected children. The mean values for numerous cardiac parameters were significantly different from normal at baseline, and most remained so throughout follow-up, with some progressing. Dilated cardiomyopathy, inadequate LV hypertrophy, and increased heart rate and blood pressure were noted. Although FS correlated with CD4 cell counts and encephalopathy at baseline, the lack of a longitudinal correlation between cardiac and immune dysfunction suggests that CD4 cell count is an inadequate surrogate for cardiac involvement in HIV-infected children. However, the development of encephalopathy was associated with a deterioration of LV function.

The global LV systolic dysfunction was due to both intrinsic cardiomyocyte dysfunction (decreased LV contractility) and abnormalities of loading conditions. Elevated afterload was persistent and related to LV dilatation, LV wall thinning, and increased blood pressure. The combination of dilatation and decreased contractility is consistent with dilated
cardiomyopathy.² The severity of LV dysfunction may be an important indicator for future survival.⁹,¹⁰,¹⁶ Most of the reduction in FS occurred during the first year of the study in patients with previously normal LV function; the fall may be partially explained by regression to the mean.

The increased LV mass appeared to result from a normal but inadequate response to persistent LV dilatation. The reduced ratio of LV thickness to dimension results in increased peak wall stress.² Elevated peak wall stress normally induces LV hypertrophy until the LV thickness-to-dimension ratio is adequate to normalize peak stress. Persistent elevation of peak wall stress indicates an inadequate hypertrophic response to LV dilatation during the follow-up interval. Growth hormone therapy has recently been suggested as a useful intervention to help improve inadequate hypertrophic responses to LV dilatation²⁵ and may be useful in these patients.

Unlike other states of malnutrition, in which LV mass falls as weight and height fall,¹⁴ LV mass for BSA was greater than normal, even though weight and height, adjusted for age and sex, were less than normal. This suggests that the demands of mechanically driven LV hypertrophy take precedence over the catabolic influence of wasting. There appears to be sparing of cardiac mass relative to skeletal muscle wasting in HIV-infected children.¹⁴

Elevation of heart rate and blood pressure may be related to the autonomic dysregulation described in HIV-infected patients.²⁶ Increased catecholamines are potent inducers of LV hypertrophy and are associated with hyperdynamic LV function acutely.²⁷ However, chronic catecholamine elevations can result in LV dysfunction.²⁷ If a hyperadrenergic state is demonstrated in these children, then an interventional trial of β-adrenergic blockade²⁸ may be warranted to determine whether the course of LV dysfunction can be altered favorably.

The baseline correlation between LV FS and encephalopathy further supports the relation between advanced neurological disease and cardiac dysfunction, an association that has also been found in other studies.⁴,¹⁷ Because of the small number of children with encephalopathy, our estimates of the magnitude of the effect of encephalopathy on LV dysfunction are not clear. However, the existence of an association is clear. Additional follow-up of this cohort may clarify the magnitude of this effect.

Immune or infectious mechanisms are likely to contribute to the myocardial damage frequently associated with dilated cardiomyopathy in HIV-infected patients.⁸,¹³ These mechanisms may include direct mononuclear immune cell activation, cytokine effects,⁸,²⁹ autoimmunity, HIV infection of myocardiocytes,³⁰ and other coinfections. Indeed, in some studies, >50% of HIV-infected adults have been noted to have myocarditis at autopsy.³¹ We found a significant correlation between FS and CD4 cell counts at baseline, but the rates of decline did not correlate with advancing HIV infection, indicating that the CD4 cell count may not be a useful surrogate marker of progressive cardiac deterioration. This conclusion is further supported in this study by both the association of encephalopathy with LV FS and the lack of an association between encephalopathy and CD4 cell count. The levels of lymphocyte subpopulations³² or combinations of surrogate markers, including the
determination of viral load, may be more useful for determining the progression of cardiac disease in HIV-infected children.

The median age of the children enrolled in this study was only 2.1 years, and they had mostly symptomatic HIV infection that did not meet CDC criteria for AIDS. A recent CDC study found that children with mildly symptomatic HIV infection had a 60% chance of developing severe symptoms within 5 years and a 35% chance of dying within 5 years.\textsuperscript{33} The mean times for the development of severe symptoms and death were 6.6 and 9.4 years, respectively.\textsuperscript{33} Most children reached a stage of moderately symptomatic HIV infection (which could include cardiomyopathy) in the second year of life and spent more than half of their lives (65 months) in this category.\textsuperscript{33} The fact that many cardiac parameters did not progress during our period of follow-up may reflect this prolonged period of moderate symptomatology. Encephalopathy indicates progression to severe symptoms. Therefore, the fall in LV function with newly diagnosed encephalopathy is related to the worsening of HIV disease.

The CD4 cell count is a correlate of the progression of the biological effects of viral infection on the immune system, but it does not sufficiently indicate the magnitude of the clinical effects.\textsuperscript{34} Several studies have shown CD4 cell count to be of limited value as a marker of clinical outcome.\textsuperscript{35,36} It appears that CD4 cell count does not mark the relationship to the putative multifactorial mechanisms proposed for the pathogenesis of HIV-associated cardiac disease. Preliminary data suggest that serial monitoring of LV function with early cardiac intervention reduces subsequent cardiac morbidity and related mortality in HIV-infected children.\textsuperscript{37} Yet the practicality, cost, characteristics of the population, and limited availability of echocardiography preclude regular cardiac monitoring for most HIV-infected children. Therefore, the importance of valid surrogate markers to increase the detection of clinically occult LV dysfunction cannot be overstated.

In summary, subclinical cardiac dysfunction is common in children with HIV infection; it may be persistent or progressive, it appears to be associated with encephalopathy, and it may affect overall survival.

**Acknowledgments**

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**Appendix 1**

Regression Equations for Cardiac Function Measures Developed From 285 Normal Infants and Children

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Equation</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS, %</td>
<td>$FS = 7.45(e^{-0.125\times\text{age}})+31.8$</td>
<td>2.52</td>
</tr>
<tr>
<td>End-diastolic dimension (EDD), cm</td>
<td>$\text{LOG EDD}=3.5(BSA^{-0.1215})+4.9$</td>
<td>0.0788</td>
</tr>
</tbody>
</table>
End-systolic dimension (ESD), cm
Log ESD=−9.4 (BSA^{−0.053})+10.4
SD=0.096

End-diastolic posterior wall thickness (WT), cm
Log WT=3.49 (BSA^{1.125})−3.83
SD=0.127

End-systolic wall stress (ESS), g/cm²
ESS=10.5 (age^{0.344})+22.5
SD=6.99

Peak systolic wall stress (PSS), g/cm²
PSS=9.4 (age^{0.567})+92.2
SD=21.2

LV mass (LVM), g
Log LVM=4.32 (BSA^{0.314})
SD=0.205

Diastolic blood pressure (DBP), mm Hg
DBP=2.84 (age^{0.641})+42.4
SD=9.07

Heart rate (HR), bpm
HR=67.2 (e^{−0.268×age})+66.3
SD = 12.5

Stress velocity index (SVI)
≤2 years old
V_{CFc}=−0.0094 [ESS (g/cm²)]+1.49
SD=0.0878

>2 years old
V_{CFc}=−0.0042 [ESS (g/cm²)]+1.25
SD=0.062

End-systolic blood pressure (ESP), mm Hg
ESP=5.17(age^{0.534})+67.5
SD = 11.28

Peak systolic blood pressure (SBP), mm Hg
SBP=2.31(age^{0.883})+85.9
SD = 10.1

Stress shortening index (SSI)
≤2 years old
FS=−0.223 [ESS (g/cm²)]+45.5
SD=2.18

>2 years old
FS=−0.211 [ESS (g/cm²)]+43.8
SD=2.176

V_{CFc} indicates heart-rate corrected velocity of circumferential fiber shortening. Units for BSA and age are square meters and years, respectively.

Appendix 2: Participants in the P2C2 HIV Study

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Ines Boechat, MD; Pamela Boyer, MD, PhD; Yvonne Bryson, MD; David Chen, MD; Joseph Church, MD; R. Dorio, MD; Robin Doroshow, MD; Stacey Drant, MD; Robert Elashoff, PhD; Alistair Fyfe, MD, PhD; Meena Garg, MD; Randall Hawkins, MD; Carl Hoh, MD; Arno Hohn, MD; Josephine Isabel-Jones, MD; Andrea Kovacs, MD; Charles Marboe, MD; Barry Marcus, MD; John Miller, MD; Arnold Platzer, MD; Robert Settlage, MD; Timothy Triche, MD; Linda Vachon, MD; Roberta Williams, MD; Marilyn Woo, MD;
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The Cleveland Clinic Foundation, Cleveland, Ohio: Mark Schluchter, PhD*; James Boyett, PhD (through 7/91)*; Barbara Baetz-Greenwalt, MD; Gerald Beck, PhD; Johanna Goldfarb, MD; Michael McHugh, MD; Atul Mehta, MD; Moulay Meziane, MD; Douglas Moodie, MD; Amrik Shah, ScD; Richard Sterba, MD; George Williams, PhD; Kenneth Abraham, BS; Cindy Chen, MS; Kirk Easley, MS; Scott Husak, BS; Victoria Konig, ART; Kevin McCarthy, RCPT; Joseph McPherson, BS; Venita Midcalf, MBA; Lisa Rybicki, MS; Paul Sartori, BS; Lori Schnur, BS; Susan Sunkle, BA, CCRA.

Consultants: Case Western Reserve University, Cleveland, Ohio: Harold Houser, MD; Richard Martin, MD.

Central Laboratory for Epstein-Barr Virus Testing

The University of Texas Health Sciences Center at San Antonio: Ciro V. Sumaya, MD* (through 12/92); Hal Jenson, MD*; Yasmin Ench, BS.

Policy, Data, and Safety Monitoring Board

Henrique Rigatto, MD (Chairman); Edward B. Clark, MD; Robert B. Cotton, MD; John Johnson, 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; Peter E. Vink, MD.

Selected Abbreviations and Acronyms

- **BSA**: body surface area
- **CDC**: Centers for Disease Control and Prevention
- **CHF**: congestive heart failure
- **FS**: fractional shortening
- **LV**: left ventricular

References


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Figure 1.
Initial echocardiographic measurements for HIV-infected infants and children plotted on regression lines with 95% prediction intervals for 285 normal children. A, LV FS percent vs age in years. B, LV end-systolic wall stress in g/cm$^2$ vs age in years. C, LV end-diastolic dimension in centimeters vs BSA in square meters. D, LV peak wall stress in g/cm$^2$ vs BSA in square meters. E, LV contractility z score vs age in years. F, Heart rate in bpm vs age in years.
Figure 2.
Longitudinal change in echocardiographic parameters by age group using repeated-measures analysis. Time trend lines represent model-based means adjusted for time on study, age, age by time on study, digitizer and baseline CD4 cell count $z$ score for LV mass and $z$ score, LV end-systolic wall stress and $z$ score, LV peak-systolic wall stress and $z$ score, and LV contractility (stress velocity index).
TABLE 1

Baseline Descriptive Statistics for 196 HIV-Infected Children

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Children</th>
<th>Percent</th>
</tr>
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<tr>
<td>Male</td>
<td>91</td>
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<tr>
<td>Female</td>
<td>105</td>
<td>53.6</td>
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<tr>
<td>Race</td>
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<td></td>
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<tr>
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<td>28</td>
<td>14.3</td>
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<tr>
<td>Black</td>
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<td>Hispanic</td>
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<td>38.8</td>
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<td>Other</td>
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<td>3.1</td>
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<td>CDC symptom status at enrollment</td>
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<tr>
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<td>40</td>
<td>20.4</td>
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<tr>
<td>AIDS, all others</td>
<td>66</td>
<td>33.7</td>
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<td>AIDS-related complex</td>
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<td>Other</td>
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<td>1.0</td>
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<td>Zidovudine</td>
<td></td>
<td></td>
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<tr>
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<td>124</td>
<td>63.3</td>
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<tr>
<td>No</td>
<td>72</td>
<td>36.7</td>
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<td>Congestive heart failure</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>2</td>
<td>1.0</td>
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<tr>
<td>No</td>
<td>194</td>
<td>99.0</td>
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<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Mean±SD</th>
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<tr>
<td>Age at echocardiogram, y</td>
<td>2.1</td>
<td>3.2±2.8</td>
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<td>Height z score (age-adjusted)</td>
<td>−1.30</td>
<td>−1.32±1.6</td>
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<tr>
<td>Weight z score (age-adjusted)</td>
<td>−1.02</td>
<td>−1.00±1.4</td>
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<tr>
<td>CD4 count, cells/mm³</td>
<td>737</td>
<td>906±890</td>
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<tr>
<td>CD4 count z score (age-adjusted)</td>
<td>−1.86</td>
<td>−1.81±1.0</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>92.0</td>
<td>92.2±11.0</td>
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<tr>
<td>Systolic blood pressure z score (age-adjusted)</td>
<td>0.00</td>
<td>0.01±1.0</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>51.0</td>
<td>52.4±10.8</td>
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<tr>
<td>Diastolic blood pressure z score (age-adjusted)</td>
<td>0.42</td>
<td>0.49±1.1</td>
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TABLE 2

Echocardiographic Measurements at Baseline Among 196 HIV-Infected Children

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
<th>Mean</th>
<th>SD</th>
<th>Expected Mean</th>
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</thead>
<tbody>
<tr>
<td>FS, %</td>
<td>196</td>
<td>-0.96</td>
<td>2.3</td>
<td>&lt;.001</td>
<td>34.6</td>
<td>6.0</td>
<td>37.0</td>
</tr>
<tr>
<td>End-diastolic dimension, cm</td>
<td>196</td>
<td>0.53</td>
<td>1.3</td>
<td>&lt;.001</td>
<td>3.14</td>
<td>0.7</td>
<td>2.95</td>
</tr>
<tr>
<td>End-systolic wall stress, g/cm²</td>
<td>181</td>
<td>0.62</td>
<td>2.1</td>
<td>&lt;.001</td>
<td>41.3</td>
<td>16.8</td>
<td>36.8</td>
</tr>
<tr>
<td>Peak-systolic wall stress, g/cm²</td>
<td>181</td>
<td>0.71</td>
<td>1.6</td>
<td>&lt;.001</td>
<td>124.2</td>
<td>37.9</td>
<td>108.8</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>192</td>
<td>0.74</td>
<td>1.1</td>
<td>&lt;.001</td>
<td>45.5</td>
<td>25.9</td>
<td>35.1</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>196</td>
<td>1.02</td>
<td>1.4</td>
<td>&lt;.001</td>
<td>114</td>
<td>23</td>
<td>101</td>
</tr>
<tr>
<td>Contractility (stress-velocity index)</td>
<td>181</td>
<td>-0.64</td>
<td>2.0</td>
<td>&lt;.001</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>
**TABLE 3**

Association of Baseline Echocardiographic Parameters With CD4 Cell Count z Score or HIV Encephalopathy Status

<table>
<thead>
<tr>
<th>Echo Parameter x Scores</th>
<th>$r_s$ With CD4 z Score (n=153)$^\dagger$</th>
<th>P</th>
<th>95% CI for $r_s$</th>
<th>Present (n=40)$^\ddagger$ Mean±SD</th>
<th>Absent (n=134)$^\ddagger$ Mean±SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS</td>
<td>0.31</td>
<td>&lt;.001</td>
<td>0.16, 0.45</td>
<td>−1.51 ±2.2</td>
<td>−0.72±2.2</td>
<td>.05</td>
</tr>
<tr>
<td>End-diastolic dimension</td>
<td>−0.35</td>
<td>&lt;.001</td>
<td>−0.49, −0.20</td>
<td>0.56±1.6</td>
<td>0.45±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic wall stress</td>
<td>−0.29</td>
<td>&lt;.001</td>
<td>−0.44, −0.13</td>
<td>1.30±2.1</td>
<td>0.38±2.1</td>
<td>.02</td>
</tr>
<tr>
<td>Peak-systolic wall stress</td>
<td>−0.13</td>
<td>NS</td>
<td>−0.29, 0.04</td>
<td>0.84±1.6</td>
<td>0.70±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass</td>
<td>−0.21</td>
<td>.009</td>
<td>−0.37, −0.05</td>
<td>0.92±1.2</td>
<td>0.64±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate</td>
<td>−0.36</td>
<td>&lt;.001</td>
<td>−0.49, −0.21</td>
<td>1.80±1.3</td>
<td>0.85±1.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Contractility (stress-velocity index)</td>
<td>0.20</td>
<td>.02</td>
<td>0.03, 0.36</td>
<td>−0.30±2.1</td>
<td>−0.76±2.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

$^*$ $r_s$ indicates Spearman rank correlation coefficient.

† Analyses restricted to lymphocyte subsets measured within 3 months of echocardiography (n=153 children).

‡ Analyses restricted to the first echocardiogram for children with encephalopathy at enrollment (n=40) and those who did not develop progressive neurological disease during the 2 years of follow-up (n=134).
### TABLE 4
Summary Statistics for Echocardiographic Measures Among 196 HIV-Infected Children

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time Since Initial Echocardiogram, mo</th>
<th>n</th>
<th>Adjusted z Score, Mean (95% CI)</th>
<th>Adjusted Raw Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS, %</td>
<td>1–3</td>
<td>196</td>
<td>−0.90 (−1.21, −0.59)</td>
<td>34.9 (34.1, 35.7)</td>
</tr>
<tr>
<td></td>
<td>3–6</td>
<td>134</td>
<td>−1.30 (−1.65, −0.95)</td>
<td>33.7 (32.8, 34.6)</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>122</td>
<td>−1.16 (−1.50, −0.83)</td>
<td>33.8 (33.0, 34.6)</td>
</tr>
<tr>
<td></td>
<td>10–14</td>
<td>113</td>
<td>−1.34 (−1.67, −1.00)</td>
<td>33.2 (32.3, 34.0)</td>
</tr>
<tr>
<td></td>
<td>14–18</td>
<td>108</td>
<td>−1.30 (−1.66, −0.95)</td>
<td>33.1 (32.2, 34.0)</td>
</tr>
<tr>
<td></td>
<td>18–22</td>
<td>103</td>
<td>−1.37 (−1.74, −0.99)</td>
<td>32.7 (31.8, 33.7)</td>
</tr>
<tr>
<td></td>
<td>22–26</td>
<td>100</td>
<td>−1.32 (−1.71, −0.93)</td>
<td>32.6 (31.7, 33.6)</td>
</tr>
<tr>
<td>End-diastolic dimension, cm</td>
<td>1–3</td>
<td>196</td>
<td>0.50 (0.34, 0.67)</td>
<td>3.09 (3.04, 3.15)</td>
</tr>
<tr>
<td></td>
<td>3–6</td>
<td>134</td>
<td>0.59 (0.40, 0.79)</td>
<td>3.20 (3.14, 3.27)</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>121</td>
<td>0.53 (0.32, 0.75)</td>
<td>3.25 (3.19, 3.32)</td>
</tr>
<tr>
<td></td>
<td>10–14</td>
<td>112</td>
<td>0.52 (0.31, 0.73)</td>
<td>3.32 (3.25, 3.38)</td>
</tr>
<tr>
<td></td>
<td>14–18</td>
<td>108</td>
<td>0.56 (0.35, 0.77)</td>
<td>3.38 (3.31, 3.44)</td>
</tr>
<tr>
<td></td>
<td>18–22</td>
<td>103</td>
<td>0.68 (0.45, 0.90)</td>
<td>3.46 (3.39, 3.52)</td>
</tr>
<tr>
<td></td>
<td>22–26</td>
<td>100</td>
<td>0.62 (0.39, 0.86)</td>
<td>3.48 (3.41, 3.55)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>1–3</td>
<td>196</td>
<td>1.01 (0.83, 1.19)</td>
<td>115.5 (113.1, 117.8)</td>
</tr>
<tr>
<td></td>
<td>3–6</td>
<td>134</td>
<td>1.14 (0.91, 1.36)</td>
<td>114.2 (111.4, 117.0)</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>123</td>
<td>1.18 (0.96, 1.40)</td>
<td>111.8 (109.0, 114.7)</td>
</tr>
<tr>
<td></td>
<td>10–14</td>
<td>115</td>
<td>1.36 (1.12, 1.60)</td>
<td>111.6 (108.6, 114.6)</td>
</tr>
<tr>
<td></td>
<td>14–18</td>
<td>109</td>
<td>1.35 (1.11, 1.59)</td>
<td>109.0 (105.9, 112.1)</td>
</tr>
<tr>
<td></td>
<td>18–22</td>
<td>103</td>
<td>1.26 (1.00, 1.51)</td>
<td>105.7 (102.4, 108.9)</td>
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<tr>
<td></td>
<td>22–26</td>
<td>100</td>
<td>1.52 (1.26, 1.78)</td>
<td>107.1 (103.8, 110.5)</td>
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<tr>
<td>LV mass, g</td>
<td>1–3</td>
<td>192</td>
<td>0.77 (0.55, 0.99)</td>
<td>44.2 (41.3, 47.1)</td>
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<tr>
<td></td>
<td>3–6</td>
<td>131</td>
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<tr>
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<td>6–10</td>
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<td>0.77 (0.53, 0.95)</td>
<td>48.2 (45.5, 50.9)</td>
</tr>
<tr>
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<td>10–14</td>
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<td>0.85 (0.70, 1.14)</td>
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</tr>
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<td>14–18</td>
<td>108</td>
<td>0.74 (0.82, 1.27)</td>
<td>52.7 (49.8, 55.1)</td>
</tr>
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<td>0.92 (0.82, 1.42)</td>
<td>56.5 (53.3, 59.6)</td>
</tr>
<tr>
<td></td>
<td>22–26</td>
<td>100</td>
<td>1.05 (0.52, 1.14)</td>
<td>60.0 (56.8, 63.2)</td>
</tr>
</tbody>
</table>

P values for comparing HIV-infected children across seven time intervals for linear trend in mean z scores are .06 for FS, .23 for end-diastolic dimension, .001 for heart rate, and .006 for LV mass. Differences in mean z scores between age groups were significant only for LV mass.
<table>
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<tr>
<th></th>
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<th>6–10</th>
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<td>Enrollment Age, y</td>
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<tr>
<td>Adjusted z score</td>
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<td>45</td>
<td>22</td>
<td>23</td>
<td>22</td>
<td>22</td>
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<tr>
<td></td>
<td>0.85±0.16</td>
<td>0.36±0.15</td>
<td>0.85±0.16</td>
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<td>0.85±0.16</td>
<td>0.36±0.15</td>
<td>0.85±0.16</td>
</tr>
<tr>
<td>Adjusted raw value, g</td>
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<td>45</td>
<td>23</td>
<td>29</td>
<td>27</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
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<td>42</td>
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<td>19</td>
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<td>Peak-systolic wall stress</td>
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<td>42</td>
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<td>43</td>
<td>42</td>
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<td>22</td>
<td>27</td>
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<tr>
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<td>0.08±0.3</td>
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<td>0.08±0.3</td>
<td>0.08±0.3</td>
<td>0.08±0.3</td>
</tr>
<tr>
<td>Adjusted raw value, g/cm²</td>
<td>&lt;1</td>
<td>57</td>
<td>57</td>
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<td>38</td>
<td>36</td>
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<td>0.15±0.3</td>
<td>0.15±0.3</td>
</tr>
<tr>
<td>Contractility (stress-velocity index)</td>
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<td>39</td>
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<td>26</td>
<td>24</td>
<td>22</td>
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### Table 5

Summary Statistics by Age for Echocardiographic Measures Among 196 HIV-Infected Children

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<th>1–3</th>
<th>3–6</th>
<th>6–10</th>
<th>10–14</th>
<th>14–18</th>
<th>18–22</th>
<th>22–26</th>
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<tr>
<td>LV mass</td>
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<td>0.8±0.2</td>
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<td>Adjusted raw value, g</td>
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<td>0.21±0.21</td>
<td>0.21±0.21</td>
<td>0.21±0.21</td>
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<td>0.6±0.3</td>
<td>0.6±0.3</td>
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<td>&lt;1</td>
<td>43</td>
<td>22</td>
<td>24</td>
<td>22</td>
<td>23</td>
<td>22</td>
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<tr>
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<td>0.08±0.3</td>
<td>0.08±0.3</td>
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<td>0.08±0.3</td>
<td>0.08±0.3</td>
<td>0.08±0.3</td>
</tr>
<tr>
<td>Adjusted raw value, g/cm²</td>
<td>&lt;1</td>
<td>57</td>
<td>41</td>
<td>38</td>
<td>36</td>
<td>37</td>
<td>27</td>
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<td>0.15±0.3</td>
<td>0.15±0.3</td>
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</tr>
<tr>
<td>Peak-systolic wall stress</td>
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<td>24</td>
<td>22</td>
<td>23</td>
<td>24</td>
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<td>−0.3±0.3</td>
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<td>−0.3±0.3</td>
<td>−0.3±0.3</td>
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</tr>
<tr>
<td>Adjusted z score</td>
<td>&lt;1</td>
<td>43</td>
<td>26</td>
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<td>22</td>
<td>23</td>
<td>24</td>
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<td>0.08±0.3</td>
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<td>0.08±0.3</td>
<td>0.08±0.3</td>
</tr>
<tr>
<td>Adjusted raw value, g/cm²</td>
<td>&lt;1</td>
<td>57</td>
<td>41</td>
<td>38</td>
<td>36</td>
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<td>0.15±0.3</td>
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</tr>
<tr>
<td>Enrollment Age, y</td>
<td>1–3</td>
<td>3–6</td>
<td>6–10</td>
<td>10–14</td>
<td>14–18</td>
<td>18–22</td>
<td>22–26</td>
</tr>
<tr>
<td>------------------</td>
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<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>Mean±SEM</td>
<td>n</td>
<td>Mean±SEM</td>
<td>n</td>
<td>Mean±SEM</td>
<td>n</td>
</tr>
<tr>
<td>2–4</td>
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<td>0.00±0.29</td>
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<td>−0.10±0.32</td>
<td>29</td>
<td>−0.70±0.30</td>
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<tr>
<td>4+</td>
<td>57</td>
<td>−0.24±0.26</td>
<td>46</td>
<td>−0.56±0.25</td>
<td>41</td>
<td>−0.44±0.26</td>
<td>38</td>
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</table>
### TABLE 6
Longitudinal Changes in FS and CD4 Cell Count z Scores (n=137 Children and 401 Echocardiograms)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS z score: intercept±SE</td>
<td>−0.61±0.16</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FS z score: slope±SE</td>
<td>−0.46±0.10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD4 cell count z score: intercept±SE</td>
<td>−1.68±0.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD4 cell count z score: slope±SE</td>
<td>−0.22±0.04</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Correlation between FS and CD4 z score slopes</td>
<td>0.14*</td>
<td>.56</td>
</tr>
<tr>
<td>Correlation between FS and CD4 z score intercepts</td>
<td>0.30†</td>
<td>.02</td>
</tr>
</tbody>
</table>

* 95% CI for the correlation between slopes: −0.36 to 0.64.
† 95% CI for the correlation between intercepts: 0.05 to 0.55.
TABLE 7
Longitudinal Changes in FS and CD4 Cell Count \( z \) Scores Stratified by HIV Encephalopathy Status (n=137 Children and 401 Echocardiograms)

<table>
<thead>
<tr>
<th>Encephalopathy</th>
<th>Not Present</th>
<th>Present Throughout Follow-up</th>
<th>Developed During Follow-up</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>( P )</td>
<td>Estimate</td>
</tr>
<tr>
<td>FS ( z ) score: intercept( \pm )SE</td>
<td>-0.50±0.18</td>
<td>.005</td>
<td>-0.93±0.39</td>
</tr>
<tr>
<td>FS ( z ) score: slope( \pm )SE</td>
<td>-0.42±0.11</td>
<td>&lt;.001</td>
<td>-0.33±0.30</td>
</tr>
<tr>
<td>CD4 cell count ( z ) score: intercept( \pm )SE</td>
<td>-1.64±0.09</td>
<td>&lt;.001</td>
<td>-1.57±0.24</td>
</tr>
<tr>
<td>CD4 cell count ( z ) score: slope( \pm )SE</td>
<td>-0.18±0.05</td>
<td>&lt;.001</td>
<td>-0.31±0.09</td>
</tr>
<tr>
<td>No. of children</td>
<td>100</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>No. of paired measurements</td>
<td>295</td>
<td></td>
<td>55</td>
</tr>
</tbody>
</table>

There is no statistical difference between the slopes among the three encephalopathy groups for FS \( z \) scores or CD4 cell count \( z \) scores.