Mild dilated cardiomyopathy and increased left ventricular mass predict mortality: The Prospective P2C2 HIV Multicenter Study

Stacy D. Fisher, Midatlantic Cardiology Associates
Kirk Easley, Emory University
E. John Orav, Brigham and Women’s Hospital
Steven D. Colan, Children’s Hospital of Boston
Samuel Kaplan, University of California Los Angeles
Thomas J. Starc, Columbia University
J. Timothy Bricker, University of Kentucky
Wyman W. Lai, Mount Sinai School of Medicine
Douglas S. Moodie, Oschner Clinic
George Sopko, National Heart, Lung, and Blood Institute

Only first 10 authors above; see publication for full author list.

Journal Title: American Heart Journal
Volume: Volume 150, Number 3
Publisher: Elsevier | 2005-09, Pages 439-447
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.ahj.2005.06.012
Permanent URL: https://pid.emory.edu/ark:/25593/rrx2b

Final published version: http://dx.doi.org/10.1016/j.ahj.2005.06.012

Copyright information:
© 2005 Mosby, Inc.
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed November 22, 2019 7:07 AM EST
Mild dilated cardiomyopathy and increased left ventricular mass predict mortality: The Prospective P2C2 HIV Multicenter Study

Stacy D. Fisher, MD\textsuperscript{a}, Kirk A. Easley, MS\textsuperscript{b}, E. John Orav, PhD\textsuperscript{c}, Steven D. Colan, MD\textsuperscript{d}, Samuel Kaplan, MD\textsuperscript{e}, Thomas J. Starc, MD\textsuperscript{f}, J. Timothy Bricker, MD\textsuperscript{g}, Wyman W. Lai, MD\textsuperscript{h}, Douglas S. Moodie, MD\textsuperscript{i}, George Sopko, MD\textsuperscript{j}, and Steven E. Lipshultz, MD\textsuperscript{k} for the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group

\textsuperscript{a}Midatlantic Cardiology Associates, Baltimore, Md

\textsuperscript{b}Department of Biostatistics, Rollins School of Public Health, Emory University, Atlanta, Ga

\textsuperscript{c}Department of Medicine, Brigham and Women's Hospital, Boston, Mass

\textsuperscript{d}Department of Cardiology, Children's Hospital, Boston, Mass

\textsuperscript{e}University of California at Los Angeles Medical Center and School of Medicine, Los Angeles, Calif

\textsuperscript{f}Division of Pediatric Cardiology, Department of Pediatrics, College of Physicians and Surgeons, Presbyterian Hospital/Columbia University, New York, NY

\textsuperscript{g}Department of Pediatrics, University of Kentucky, Lexington, Ken

\textsuperscript{i}Division of Pediatric Cardiology, Department of Pediatrics, Mount Sinai School of Medicine, New York, NY

\textsuperscript{j}Department of Pediatrics, Oschner Clinic, New Orleans, La

\textsuperscript{k}National Heart, Lung, and Blood Institute, Bethesda, Md

\textsuperscript{l}Department of Pediatrics, University of Miami Miller School of Medicine, Miami, Fla

Abstract

\textbf{Background}—Many HIV-infected children die with cardiac abnormalities. We sought to understand the course of these HIV-associated abnormalities and their impact on all-cause mortality.

\textbf{Methods}—We describe longitudinal changes in left ventricular (LV) structure and function and mortality in 185 children vertically infected with HIV. Serial cardiac data were obtained from 0.1 to 10 years of age. Age- or body surface area–adjusted \( z \) scores were calculated for 10 echocardiographic outcomes.

© 2005, Mosby, Inc. All rights reserved.
Reprint requests: Steven E. Lipshultz, MD, Department of Pediatrics (D820), University of Miami Miller School of Medicine, PO Box 018820, Miami, FL 33101. Express mail address: Department of Pediatrics, University of Miami Miller School of Medicine, Medical Campus-MCCD-D820, 1601 NW 12th Avenue, 9th Floor, Miami, FL 33136., slipshultz@med.miami.edu.
Results—Median age at first echocardiogram was 2 years (range 0.2–9.4 years); median follow-up was 3.6 years (range 0–6.3 years). The 5-year cumulative incidence of congestive heart failure was 12.3%. Mean fractional shortening z scores declined from −0.65 at 1 year of age to −1.47 at 3 years of age without further decline between 3 and 10 years of age. Among children with 2 echocardiograms performed in the first year of follow-up, mild LV dysfunction (fractional shortening of <−2 SD on both echocardiograms) was present in 29 (18%) of 158 children. For these 29 children, the 5-year mortality was 55.4%. Left ventricular mass z scores were elevated at 1 year (mean z score 0.68, \( P < .001 \)) and remained elevated throughout follow-up. In the 8 children with LV mass z score of >2 SD on both initial and follow-up echocardiograms, the 5-year mortality was 75%.

Conclusion—In HIV-infected children, LV structure and function progressively deteriorated in the first 3 years of life, resulting in subsequent persistent mild LV dysfunction and increased LV mass. Chronic mild depression of LV function and elevated LV mass were associated with higher all-cause mortality.

Many children with vertically transmitted HIV infection generally have depressed left ventricular (LV) function as measured by either fractional shortening (FS) or contractility, as well as increased LV wall thickness or calculated mass normalized for body surface area at birth.\(^1\) Both normalized depressed LV function and increased LV mass are persistent and often progressive during the first 2 to 3 years of follow-up.\(^1\)–\(^4\) In HIV-infected children, these mild echocardiographic abnormalities are independently predictive of both cardiovascular and all-cause mortality.\(^5\),\(^6\) In other patient populations, moderate or severe LV dysfunction or hypertrophy affects cardiac mortality but mild abnormalities have not been assessed.

The concept of low-level, subclinical LV dysfunction and growth affecting mortality warrants further investigation, especially because the mean life expectancy for HIV-infected children is increasing.\(^7\) In the era before highly active antiretroviral therapy (HAART), the mean life expectancy was 9 years.\(^8\) Longevity improved with new therapies.\(^7\) Therefore, we need to better understand the cardiovascular abnormalities that develop in these children with longer periods of follow-up to formulate effective preventive and therapeutic strategies.

Understanding the long-term nature and course of cardiac disease related to HIV infection will also provide a platform on which to evaluate the benefits and risks of new therapies such as HAART. Because compliance with and availability of HAART are quite limited worldwide, patient data of the pre-HAART era remain applicable.\(^9\) Furthermore, AIDS-related cardiomyopathy might serve as a model for the effects of long-term immunosuppression and infection on the heart, thereby expanding our current understanding of the etiologies and pathogenesis of such cardiomyopathy.

Our prior work\(^6\) on the impact of abnormalities of echocardiographically derived measurements on mortality was limited to a single set of measurements made at baseline enrollment in the P\(^2\)C\(^2\) HIV study, and follow-up was limited. Final data are now available from the P\(^2\)C\(^2\) HIV study, in which a cohort of HIV-infected children was followed up to 10 years of age. The patients were enrolled before HAART was in widespread use, which means that these data can be applied broadly to many patients within the United States and
most patients outside the United States who do not have access to HAART. This article, which contains the final data, specifically evaluates the stability or progression of LV dysfunction and determines the relationship between dysfunction and mortality to identify high-risk subpopulations.

Methods

The protocol of the P$^{2}$C$^{2}$ HIV study has been described previously. The present study was limited to children of >28 days of age (n = 205) with documented vertically transmitted HIV infection; they were enrolled between May 1990 and April 1993 in a prospective observational study. Cohort characteristics have been reported. Serial echocardiographic evaluations were performed at 5 clinical centers in the United States at protocol-specified intervals of every 4 months. The data were remeasured at a central location to ensure that they were uniform. The central laboratory was not aware of the patients’ clinical status or therapy.

Patient history, including the incidence of congestive heart failure, was prospectively obtained during clinic visits or by review of medical records. The diagnosis of congestive heart failure was determined by a pediatric cardiologist at each center and was based on the child’s clinical findings. Disease status was classified at the time of echocardiography. Two-dimensional echocardiography and Doppler studies with stress-velocity analysis of LV contractility were performed for each child.

For the current article, we focused on 10 echocardiographic outcomes: (1) LV FS, (2) heart rate, (3) LV mass, (4) LV end-diastolic posterior wall thickness, (5) LV contractility, (6) LV end-diastolic dimension, (7) LV end-systolic dimension, (8) LV thickness-dimension ratio, (9) LV meridional end-systolic LV wall stress (afterload), and (10) LV peak-systolic wall stress. Left ventricular contractility was determined from the relationship between end-systolic LV wall stress and the rate-adjusted velocity of fiber shortening, and was defined as the standardized difference between the observed and the expected values of the rate-adjusted velocity of fiber shortening.

Normal values for each of the 10 echocardiographic measures by age or body surface area were developed by obtaining cross-sectional data from a separate external comparison group consisting of 285 healthy infants and children seen in the noninvasive laboratory at Children’s Hospital, Boston, for echocardiographic evaluation during the years 1987 to 1998, who had no evidence of structural or functional heart disease. Acquired or congenital heart disease and other systemic disorders were excluded by a careful review of the medical history, electrocardiogram, chest x-ray, and echocardiogram. Specific exclusion criteria included acute or chronic systemic disorder, hypertension, a family history of hypertrophic or dilated cardiomyopathy, and height or weight percentile outside the range of normal. The study of these healthy control subjects was conducted under a protocol approved by the institutional review board in 1985. The data were measured at the same central digitizing facility in the same manner as the study patient data.
Age correction was used for FS, wall stress, and heart rate, and body surface area correction was used for LV dimension, mass, end-diastolic posterior wall thickness, and the thickness-dimension ratio. Regression equations for cardiac structure and function measures developed from the external control subjects for these studies are listed in the study by Lipshultz et al. Informed consent was obtained from the HIV-infected children, their parents, or guardians as part of protocols approved by institutional review boards at all institutions.

**Statistical methods**

To assess whether the echocardiographic changes occurred over time, repeated-measures analyses for each of the 10 echocardiographic measurements and z scores were performed using a means model with SAS Proc Mixed (SAS Institute Inc, Cary, NC), which provided separate estimates of the means by age (10 one-year age intervals: 1 month to 1 year plus 9 one-year intervals until the age of 10 years). A heterogeneous compound symmetry variance-covariance from among the repeated measurements was assumed for each outcome, and robust estimates of the SEs of parameters were used to perform tests and construct 95% CIs. All statistical tests were 2-tailed, and a P value of ≤0.05 was considered to indicate statistical significance for the age effect for the repeated-measures analysis of each echocardiographic z score. A Bonferroni adjustment (P ≤ 0.005) was used to compare the mean z score for each cardiac measurement with a z score of 0 at each of the 10 age intervals.

Cumulative mortality and cumulative rate of congestive heart failure were estimated with the Kaplan-Meier method. In a subset of 158 children with 2 echocardiograms performed in the first year of follow-up, 5-year cumulative mortality rates were estimated by z score categories for FS (z scores of >0, 0 to −2, and ≤−2) and LV mass (z scores of ≤0, 0–2, and >2). Mortality rates were estimated using both the first and second echocardiogram. Fractional shortening z score categories were “depressed” (z scores of <−2 on both echocardiograms), “low normal” (z scores from 0 to −2 on both echocardiograms), and “high normal” (z scores of >0 on both echocardiograms or z score of >0 on the first echocardiogram and z score from 0 to −2 on the second echocardiogram).

Left ventricular mass z score categories were “elevated” (z scores of >2 on both echocardiograms), “high normal” (z scores of 0–2 on both echocardiograms), and “low normal” (z scores of <0 on both echocardiograms or z score of <0 on the first echocardiogram and 0–2 on the second echocardiogram). Log-rank tests were used to compare mortality by degree of LV dysfunction and LV mass elevation.

**Results**

Of the 205 patients enrolled of >28 days of age who were enrolled on the P2C2 HIV study, 193 had echocardiograms of sufficient quality to be remeasured at the central facility that were available for analysis. Because very few echocardiograms were available after the age of 10 years, we excluded 8 children who were >10 years of age at enrollment. Therefore, data from 185 children were used in this analysis.
Participants were followed for a median of 3.6 years, and a median of 9 echocardiograms per subject were available for analysis. Echocardiography was performed within 3 months of enrollment in 68.1% of participants. The age at initial echocardiography was >1 month and <1 year in 23.8%, 1 to 2 years in 24.9%, 2 to 3 years in 14%, 3 to 4 years in 10.8%, 4 to 5 years in 9.7%, 5 to 6 years in 5.9%, 6 to 7 years in 5.4%, 7 to 8 years in 2.1%, 8 to 9 years in 2.2%, and 9 to 10 years in 1.1% (median age at first echocardiogram 2 years). Echocardiography was performed in 44 infants by 1 year of age.

Demographics
Eighty-three of the children were African American (45%), and 68 were Hispanic (37%). Most had symptomatic HIV infection as characterized by immunosuppression and reduced height and weight at enrollment. More than half (56.2%) of the patients had taken zidovudine before enrollment, and by the end of the follow up, 92.4% had received the drug. Ten percent of the patients received an angiotensin-converting enzyme inhibitor at any time during the study (19/185), including 3 children who received captopril, 14 who received enalapril, and 2 who received both (but not at the same time). No patient was on a β-blocker. After 2 patients with symptomatic congestive heart failure at enrollment were excluded, the 5-year cumulative incidence of congestive heart failure was 12.3%. The 5-year cumulative mortality was 31.7% (SE 3.6%, median follow-up 61.7 months).

Longitudinal results
Fractional shortening—As illustrated in parts A and B of Figure 1, FS was depressed compared with that of control children throughout the first 10 years of age (P < .001). The HIV-infected children had an initial mean FS measurement of 36.9%, which was approximately 0.65 SD lower than that of the control subjects in 65 HIV-infected children <1 year of age (P = .01). This difference did not reach significance at the Bonferroni-corrected level of .005. However, by the age of 2 years, the mean FS had fallen to 35.0%, which was significantly lower than that of the control subjects (FS z score −1.12, P < .001). Between ages 2 and 10 years, FS fluctuated between 1 and 1.5 SD lower than that of the control subjects. Although the FS was significantly depressed at each year of age (P < .001), there was no tendency toward further worsening or improvement (P = .11 for overall differences by age).

Heart rate—Heart rates in the HIV-infected children were significantly elevated at each age of observation (P < .001 for each age interval) compared with those in the control children. Heart rate z scores continued to increase and became more abnormal with age (P = .03 for overall differences by age and P = .004 for linear trend). As shown in part A of Figure 2, the mean heart rate z score increased from 1.03 in the children who were <1 year of age to 1.78 in the children who were approximately 10 years of age. Actual mean heart rates were 134 beats/min in children ≤1 year of age (expected heart rate 118 beats/min) and 94 beats/min in children who were 9.5 to 10.5 years old (expected heart rate 71 beats/min).

Left ventricular mass—Left ventricular mass was significantly elevated at each age of observation (P < .001) compared with that of the control subjects. The extent of the elevation depended on age (P = .01). However, unlike heart rate, which progressively rose
over time, LV mass was most abnormal in the children who were approximately 3 to 4 years old (mean LV mass $z$ scores of 0.85 and 0.84, respectively). As the children became older, LV mass fell slightly to a persistent elevation of about 0.5 SD more than that of the control subjects (Figure 2, B).

**Left ventricular wall thickness**—Left ventricular wall thickness declined in the first 4 years followed by a gradual rise. Mean $z$ scores were persistently lower than those of the control subjects; the most significant thinning was evident during years 2 through 6 (Figure 2, C). During the first year of life and during years 7, 9, and 10, the differences in LV wall thickness between the HIV-infected children and the control children were not statistically significant, although the fluctuations in the data did not permit any assessment of an age-dependent pattern ($P = .39$).

**Left ventricular contractility**—Contractility followed the same pattern as FS: it was moderately but nonsignificantly depressed during the first year of life ($z$ score $-0.41$, $P = .02$) but was significantly depressed throughout the rest of the age groups ($P < .001$). Unlike FS, where the depression was relatively consistent across ages, LV contractility fluctuated with age ($P = .001$) (Figure 2, B) and was severely depressed in the HIV-infected children around the age of 2 years and again around the age of 10 years.

**Left ventricular end-diastolic and end-systolic dimensions**—Both end-diastolic and end-systolic LV dimensions were significantly higher than those of the control children at all ages ($P < .001$). In addition, both changed significantly and in similar patterns over time ($P = .002$ for end-diastolic dimension, $P = .004$ for end-systolic dimension). Both dimensions became progressively elevated during the first 4 years of life and then stabilized or even possibly improved by the age of 9 years (Figure 2, E and F, respectively).

**Left ventricular thickness-dimension ratio**—The LV thickness-dimension ratio $z$ score over time was significantly reduced ($P = .005$) and changed from normal to being depressed during the first 2 years of life, indicating inadequate LV hypertrophy for the LV dimension. The mean LV thickness-dimension ratio $z$ scores on the first 2 echocardiograms were $-0.336$ and $-0.59$.

**End-systolic and peak-systolic wall stress**—Both end-systolic and peak-systolic wall stresses were significantly higher in the HIV-infected children who were between the ages of 3 and 7 years compared with those of the control children ($P < .001$). The elevation in peak-systolic wall stress also extends to children who are 2 and 8 years of age. However, the youngest and oldest children did not have significantly elevated wall stresses, and the progressively peaked pattern in the children of the middle age groups was both statistically significant ($P < .001$ for each wall stress) and clearly evident as shown in parts G and H of Figure 2.

**Effect on all-cause mortality**

**Left ventricular fractional shortening**—Table I shows the mortality rates for the subset of 158 HIV-infected children who had at least 2 echocardiograms in the first year of
follow-up; they are divided according to their first 2 measured FS z scores. Crude mortality rates varied from 15% to 20% in children whose initial FS was more than the normal mean at the start (z score >0) and remained in the normal range 4 months later (z score >−2). It was 20% to 30% in children who either started with more than the normal mean (z score >0) but had a steep decline (z score <-2) or who started with close to but less than the normal mean (−2 < z score < 0), and it was 30% to 60% in children with mildly depressed FS (z score <-2) at the outset.

Kaplan-Meier 5-year mortality estimates are also shown in Table I for the 3 largest and most interpretable subgroups. The children with high-normal FS at baseline and normal FS at follow-up had the lowest 5-year mortality (15.4%), whereas the children with FS that was persistently lower than that of the control subjects but still in the normal range had a 28.3% 5-year mortality rate. The children with persistent mildly depressed FS had a 55.4% 5-year mortality. These differences, which were statistically significant (P < .001) as determined by the log-rank test, are displayed in part A of Figure 3.

**Left ventricular mass**—The second half of Table I shows similar results for the subgroup of 158 HIV-infected children divided according to their first 2 measured LV mass z scores. There were significant survival differences (P < .001) between 3 groups: children whose LV mass was lower than that of the control subjects at baseline but within the normal range at follow-up (estimated 5-year mortality 23.6%), children with LV mass that was persistently more than that of the control subjects but within the normal range (estimated 5-year mortality 30.7%), and children with an LV mass that was persistently and mildly elevated (estimated 5-year mortality 75%). Kaplan-Meier curves illustrating these mortality differences are shown in part B of Figure 3.

**Left ventricular thickness-dimension ratio**—Only 3 children had a LV thickness-dimension ratio z score of <-2 on both echocardiograms, and 2 died. The P value from the log-rank test comparing the 3 survival curves for degrees of reduction in the thickness-dimension ratio was .11. There were 8 children with an LV thickness-dimension ratio z score of >1 on both echocardiograms. There were no differences in the mortality curves (P = .76) when divided by degree of elevation of the thickness-dimension ratio (data not shown).

**Discussion**

Our longitudinal follow-up of HIV-infected children shows that, although cardiac function was mildly depressed and LV dimension and mass were inappropriately high on initial evaluation, sequential echocardiographic measures of both cardiac structure and function were stable over time.

The effect of mild chronic depression of LV systolic function is largely unexplored in HIV-related cardiac disease and in general heart failure populations. A striking finding from short-term follow-up in the P^2C^2 HIV study is that even a mild abnormality in either FS depression or LV mass elevation is independently and significantly associated with all-cause mortality.1^4 Progressive deterioration of LV function was expected in long-term survivors.
based on early data. Instead, we initially observed mild chronic LV systolic dysfunction in long-term survivors and increased LV mass, which remained relatively stable over time and associated with all-cause mortality. These findings may be applicable to patients with idiopathic cardiomyopathy and patients with heart failure who do not regain normal systolic function even with treatment.

Malnutrition and wasting are associated with increased cardiovascular mortality in HIV-infected children. An inverse relationship has been demonstrated between heart rate and nutritional status suggesting an increase in the basal metabolic rate with interdependent effects of malnutrition, altered cardiac muscle mass, and LV dysfunction. The early manifestation and subsequent persistence of mild changes in cardiac structure and function in the setting of increased sympathetic drive may explain the increase in symptomatic congestive heart failure and cardiovascular mortality in advanced HIV disease.

This study supports the concept that we developed in the separate P<sup>2</sup>C<sup>2</sup> HIV birth cohort study that an early myocardial insult occurs in children born to HIV-infected mothers. From our other cohort, we speculated that development in an unhealthy uterine environment was associated with neonatal dilated cardiomyopathy regardless of neonatal HIV status that remained persistent with up to 5 years of follow-up. In this independent cohort of HIV-infected children, we extend that observation for up to 10 years of HIV infection and have been able to characterize the course of largely asymptomatic mild dilated cardiomyopathy in early childhood.

We found a progressive fall in FS during the first 3 years of life that subsequently stabilized. The early afterload excess over the first 4 years of life was due to LV dilation and wall thinning. Mechanical signaling to increase LV hypertrophy remained most highly elevated during the first 4 years until LV thickness normalized. Left ventricular mass remained stably elevated but trended toward normalization ≥7 years after birth. With elevated peak-systolic stress resulting in increased LV thickness in the setting of an increased dimension, z scores normalized late and there was lack of progressive dilation with increasing somatic growth. This appears different from other models of dilated cardiomyopathy where chronic afterload excess is often progressive.

Although LV mass was elevated and the elevation in mass related to outcome, the magnitude of hypertrophy was still inadequate, as evidenced by the persistent significant elevation of peak-systolic wall stress. That is, LV wall thickness was decreased although LV dimension was elevated. We looked at the LV thickness-dimension ratio as an index of inadequate hypertrophy and found that it was not helpful in risk assessment. Thus, the magnitude of the inadequate hypertrophy did not predict outcome. There are data to suggest that hypertrophy is detrimental and other data that suggest that chronic elevation of wall stress as a marker of the adequacy of hypertrophy is detrimental. Because more hypertrophy will reduce wall stress, there would, in theory, be a tradeoff of one for the other. We found that hypertrophy was predictive but the LV thickness-dimension ratio and LV wall stress were not, suggesting that hypertrophy alone is more important in determining mortality than is either the adequacy of hypertrophy relative to the LV dimension or to the degree of LV wall stress.
Fractional shortening became depressed at a young age but did not become worse. This was due to the combined effect of slowly progressive impairment of LV contractility along with an initially excessive afterload that improved with age. The progressive depressed contractility and tachycardia are very concerning because they suggest that an early prenatal myocardial perturbation results in pervasive, persistent, and progressive LV dysfunction with augmentation of cardiac output occurring because of increasing heart rate in the setting of falling contractility. This pattern is even more problematic because it has occurred even with informative censoring because of loss of patients with the most impairment. This suggests that even in the healthiest patients, symptomatic ventricular dysfunction is a likely future occurrence with increasing age. This study is unique because it shows the relative impact of very mild LV dysfunction or increased LV mass on subsequent mortality in children from 1 month to 10 years of age. A depressed LV FS of 2 SD lower than normal is associated with excess mortality. For a 10-year-old child with a normal FS of 34%, a 2 SD drop represents a drop of 4 FS points to 30%. Routine clinical practice has not usually placed much clinical significance on such a small drop. Yet, for this population, even such a small drop is associated with a highly significant large increase in 5-year mortality. Similar findings are observed for the clinically significant small increases in LV mass resulting in excess mortality in this population. This indicates a need for developing and evaluating targeted interventions. This also suggests that children with very mild LV dysfunction or excess LV hypertrophy who do not have HIV infection need further investigations to determine if these abnormalities in early life are associated with a similar course and clinical implication as in this population.

The effects of early perinatal myocardial impairment loom large over time with ominous prognostic implications. Our work has found that, even in healthy neonates born to HIV-healthy mothers, significant myocardial injury can be detected in the neonatal period that may relate to perinatal health status. Although clinically occult, such injury can result in transient ventricular dysfunction for some patients and more permanent dysfunction for other patients. We used serial echocardiograms to differentiate transient from chronic LV dysfunction and showed that transient LV dysfunction is not associated with the same high degree of excess mortality that we have observed with chronic LV dysfunction. This work further suggests that the fetal and perinatal periods may be very important ages to protect the myocardium from insults.

Study limitations

There are several limitations in our study. The effect of informative censoring due to progressive mortality cannot be accurately determined. If that effect was significant, it might explain the reduction in afterload and improvements in LV thickness and dimension. However, if that effect was significant, it would also suggest that the magnitude we have observed of progressive abnormalities of LV contractility and heart rate are less than what is true.

Cardiac death has been reported as the underlying cause of death in 12% of patients in this cohort. Cardiac-specific mortality is not presented in this analysis because of a small sample size, and data presented are limited to all-cause mortality. A third limitation stems
from the selection of the external control group. Our study was initially designed to recruit a control sample of mothers with similar demographics except without HIV infection during pregnancy, but this was not feasible. As a result, we recruited an external control sample that may not be ideally matched for socioeconomic and other relevant factors, is cross-sectional, and has a limited number of patients. A small number of patients received angiotensin-converting enzyme inhibitor therapy at some time during this study. Therefore, cardiac measurements and outcomes could reflect both natural progress and treatment. Also, the cardiac abnormalities that we have seen in the HIV-infected cohort and have attributed to progressive HIV could have been caused by other mechanisms such as anemia, coinfections, malnutrition, renal dysfunction, and hypertension. Although our prior work suggests that these factors do not significantly alter our outcomes, we cannot eliminate such possibilities entirely. Finally, this study was limited to examinations of cardiac structure and function in patients who were alive at each age. The initially abrupt fall in FS and increase in LV chamber size may be related to rapidly progressive illness with HIV that may have been incompletely captured by protocol-defined echocardiographic examinations at set intervals.

Conclusion

We observed mild persistent cardiac dysfunction in the HIV-infected children that was accompanied by elevated rates of clinical congestive heart failure and mortality. However, stabilization of FS did not necessarily reduce mortality rates to those of patients with normal cardiac function.

Our study suggests that persistent mild LV dysfunction, at levels that most cardiologists would not consider to be action values, has important prognostic implications. We establish persistent mild LV dysfunction and mildly increased LV mass as risk markers for early mortality in HIV disease. This study suggests that 2 serial echocardiograms in the first year of life in this population have prognostic implications and should be considered for clinical care. Further research is needed to determine if earlier detection prompting earlier therapy results in improved outcomes.

Acknowledgments

This work was supported by the National Heart, Lung, and Blood Institute, Bethesda, Md (N01-HR-96037, NO1-HR-96038, NO1-HR-96039, NO1-HR-96040, NO1-HR-96041, NO1-HR-96042, NO1-HR-96043), and in part by the National Institutes of Health General Clinical Research Center (Bethesda, Md) grants (RR-00188, RR-00533, RR-00071, RR-00645, RR-00865, and RR-00043).

We dedicate this work to the memory of our esteemed colleague, Samuel Kaplan, MD, who led the P2C2 HIV Study Cardiology Subcommittee from 1989 until his death in 2004.

References


Appendix A

A complete list of study participants can be found in Reference [10].

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Hannah Peavy, MD (Project Officer); Anthony Kalica, PhD; Elaine Sloand, MD; George Sopko, MD, MPH; Margaret Wu, PhD

CHAIRMAN OF THE STEERING COMMITTEE: Robert Mellins, MD

CLINICAL CENTERS

Baylor College of Medicine, Houston, Tex
William Shearer, MD, PhD; Nancy Ayres, MD; J Timothy Bricker, MD; Arthur Garson, MD; Linda Davis, RN, BSN; Paula Feinman; Mary Beth Mauer, RN, BSN; University of Texas: Debra Mooneyham, RN; Teresa Tonsberg, RN

The Children’s Hospital, Boston/Harvard Medical School, Boston, Mass

Steven Lipshultz, MD; Steven Colan, MD; Lisa Hornberger, MD; Stephen Sanders, MD; Marcy Schwartz, MD; Helen Donovan; Janice Hunter, MS, RN; Ellen McAuliffe, BSN; Nandini Moorthy; Patricia Ray, BS; Sonia Sharma, BS; Boston Medical Center: Karen Lewis, RN

Mount Sinai School of Medicine, New York, NY

Meyer Kattan, MD; Wyman Lai, MD, MPH; Diane Carp, MSN, RN; Donna Lewis; Sue Mone, MS; Beth Israel Medical Center: Mary Ann Worth, RN

Presbyterian Hospital in the City of New York/Columbia University, New York, NY

Robert Mellins, MD; Fred Bierman, MD (through May 1991); Thomas Starc, MD, MPH; Anthony Brown; Margaret Challenger; Kim Geromanos, MS, RN

University of California at Los Angeles School of Medicine, Los Angeles, Calif

Samuel Kaplan, MD; Y Al-Khatib, MD; Robin Doroshow, MD; Josephine Isabel-Jones, MD; Roberta Williams, MD; Helene Cohen, RN, PNP; Sharon Golden, RDMS; Karen Simandle, RDMS; Ah-Lin Wong, RDMS; Children’s Hospital, Los Angeles: Arno Hohn, MD; Barry Marcus, MD; Audrey Gardener, BS; Toni Ziolkowski, RN; Los Angeles County Hospital/University of Southern California: Lynn Fukushima, MSN, RN

CLINICAL COORDINATING CENTER

The Cleveland Clinic Foundation, Cleveland, Ohio

Kirk A. Easley, MS; Michael Kutner, PhD (through December 1999); Mark Schluchter, PhD (through April 1998); Johanna Goldfarb, MD; Douglas Moodie, MD; Cindy Chen, MS; Scott Husak, BS; Victoria Konig, ART; Sunil Rao, PhD; Paul Sartori, BS; Lori Schnur, BS; Amrik Shah, ScD; Sharayu Shanbhag, BSc; Susan Sunkle, BA, CCRA; Weihong Zhang, MS

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; Peter E. Vink, MD

---

1Principal investigator.
Figure 1.
A. Longitudinal change in mean LV FS (%) in 185 HIV-infected children and cross-sectional mean FS for 285 control children. B. Summary of the longitudinal change in mean LV FS z score for the 185 HIV-infected children. The vertical bars represent the 95% CIs for the means. Sample sizes at the bottom are the number of echocardiograms performed at each age.
Figure 2.
Figure 3.
A. Cumulative mortality among 113 HIV-infected children by degree of LV dysfunction. Twenty-nine patients had a depressed FS $z$ score ($<-2$ on both studies), 51 had a high-normal $z$ score (>0 on their first 2 sequential echocardiograms or >0 on the first echocardiogram and 0 to −2 on the second study), and 33 had a low-normal $z$ score (0 to −2 on both studies). Mortality was highest in those with a depressed $z$ score. B. Cumulative mortality among 118 HIV-infected children by LV mass $z$ score. Eight children had an elevated LV mass $z$ score (>2 on both studies), 35 had a low-normal $z$ score (<0 on their first 2 sequential echocardiograms or a $z$ score of <0 on the first echocardiogram and 0–2 on the second study), and 75 had a high-normal $z$ score (0–2 on both studies). Mortality was highest in those with an elevated $z$ score.
<table>
<thead>
<tr>
<th>Echocardiogram z score</th>
<th>Children n</th>
<th>Deaths n</th>
<th>5-y* cumulative mortality ± SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First and second</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0 and &gt;0</td>
<td>28</td>
<td>5</td>
<td>15.4 ± 5.4†</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>≥0 and 0 to −2</td>
<td>23</td>
<td>3</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>≥0 and ≤−2</td>
<td>7</td>
<td>2</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>0 to −2 and &gt;0</td>
<td>9</td>
<td>2</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>0 to −2 and 0 to −2</td>
<td>33</td>
<td>9</td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td>0 to −2 and ≤−2</td>
<td>13</td>
<td>4</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>≤−2 and &gt;0</td>
<td>4</td>
<td>2</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>≤−2 and 0 to −2</td>
<td>12</td>
<td>4</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>≤−2 and ≤−2</td>
<td>29</td>
<td>17</td>
<td>58.6</td>
<td></td>
</tr>
<tr>
<td>0–2 and 0–2</td>
<td>75</td>
<td>20</td>
<td>26.7</td>
<td></td>
</tr>
<tr>
<td>0–2 and 0</td>
<td>75</td>
<td>20</td>
<td>26.7</td>
<td></td>
</tr>
<tr>
<td>0–2 and &gt;2</td>
<td>9</td>
<td>2</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>≤2 and ≤0</td>
<td>10</td>
<td>8</td>
<td>80.0</td>
<td></td>
</tr>
<tr>
<td>&gt;2 and 0–2</td>
<td>10</td>
<td>8</td>
<td>80.0</td>
<td></td>
</tr>
<tr>
<td>&gt;2 and &gt;2</td>
<td>8</td>
<td>6</td>
<td>75.0</td>
<td></td>
</tr>
</tbody>
</table>

* Cumulative mortality estimates provided for the 3 subgroups summarized in Figure 3.
† 5-year cumulative mortality based on the first 2 z score categories that represent the high-normal subgroup for FS.
‡ P value for the log-rank test comparing cumulative mortality between the 3 subgroups graphically summarized in Figure 3.
§ 5-year cumulative mortality based on the first 2 z score categories that represent the low-normal subgroup for LV mass.

Table I
Cumulative mortality according to echocardiographic measurements made in the first year of follow-up (n = 158 children)