Presentation: H-2312

Prevalence of Pulmonary Hypertension in Asymptomatic HIV-infected Patients Receiving Antiretroviral Therapy

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ABSTRACT

Background: HIV infection has been implicated as an independent risk factor for pulmonary arterial hypertension (PAH). It has been suggested that antiretroviral therapy (ART) may decrease PAH-related mortality. Our objective was to determine the prevalence of PAH in a cohort of HIV infected pts without pulmonary or cardiovascular (CV) symptoms receiving ART.
Methods: A cross-sectional study of HIV-infected pts at the National Naval Medical Center was conducted. Clinical data including demographics, HIV factors, cardiac risk factors (CRF) and ART were collected. Each pt underwent a 2-D transthoracic echocardiogram utilizing standard and tissue Doppler techniques. HIV prognostic indicators (AIDS progression risk), cumulative ART, and CRF were assessed for their association with PAH (PA systolic pressure $\geq$ 35mmHg).
Results: 91 pts with the following characteristics were enrolled: age: 37$\pm$7 yrs; duration of HIV infection: 10.8$\pm$6 yrs; CD4 cell count: 583$\pm$285 cells/mm^3; ART duration: 5.4$\pm$3.3 yrs. PAH was observed in 5 pts (5.5%;95% CI 1.81-12.36) with a median pressure 36mmHg (IQR 36 -37 mmHg). No association with HIV factors or CRF was observed. Diastolic dysfunction was more common in pts with PAH, 60 vs. 36%, however this was not statistically significant. There was no difference with respect to PI use, AIDS risk score, or CD4 nadir in pts with or without PAH.
Conclusion: This cohort of asymptomatic well controlled HIV pts on ART at low risk for AIDS and CV disease had a 5.5% rate of PAH. When present, PAH was mild and asymptomatic. The prevalence is much higher than reported rates in HIV uninfected pts of similar age and is slightly lower than rates reported in symptomatic AIDS patients. Our findings were unexpected in our asymptomatic cohort. It is yet to be determined if ART effects PAH incidence or prognosis.

INTRODUCTION

Pulmonary Arterial Hypertension and HIV infection:

- HIV has been implicated as an independent risk factor for PAH.
- The prevalence of symptomatic PAH in HIV infection has been estimated between 0.06-2%, with a three year mortality of those with New York Heart Association functional class III-IV of 72%. Recently, there have been reports of high prevalence of asymptomatic PAH in well controlled HIV infected pts. However, this cohort had a large portion of intravenous drug users, which has a known association with PAH.
- Conflicting data exists as to whether ART decreases the incidence of PAH. In addition, it has been suggested that ART may have a beneficial effect in HIV infected pts with PAH.

Pulmonary Arterial Hypertension:

- While right heart catheterization is considered the goal standard to diagnosis PAH, transthoracic echocardiography (TTE) is the preferred non-invasive method to evaluate for PAH along with evaluation of its consequences and potential causes.
- PAH has variable definitions with a pulmonary artery systolic pressures (PSAP) ranging anywhere from greater than 30 to 50mmHg. Generally speaking, a PASP of > than 35 mmHg has been considered to be consistent with mild PAH.

Objective:
- To determine the prevalence of PAH in a cohort of HIV infected pts without pulmonary or cardiovascular symptoms receiving ART using TTE.

METHODS

- Cross-sectional, single-center study
- Designed to estimate the prevalence of cardiac diastolic dysfunction in an asymptomatic cohort of HIV infected patients on combination ART. A sub-study analysis was done to estimate the prevalence of PAH in this cohort.
- Patients enrolled by health care providers in the HIV clinic at the National Naval Medical Center at the time of routine follow-up
- All patients were asymptomatic for ischemic heart disease or congestive heart failure
- Ages 18 to 50, male and female.
- Exclusion criteria: known coronary artery disease, cardiomyopathy, peripheral or cerebrovascular disease, current, active AIDS
- Clinical data: medical records reviewed by C.D. and pertinent data on HIV status and cardiac risk factors collected. An AIDS Risk Score was calculated based on risk levels derived from a well-validated study.[6] This score utilizes CD4 cell count, viral load, CDC Stage (A,B,C), and sociodemographic factors to stratify the probability of progressing to AIDS or death at one to three years from the time of analysis. "Low" is < 5%, "Medium" is 5-15%, and "High" is > 15%.
- Echocardiography Data: Transthoracic echocardiography performed by one of two designated sonographers using Hewlett Packard 2000 machines. Studies interpreted independently by two cardiologists (G.N and M.F.) masked to clinical data. Full two dimensional and Doppler assessments were performed. Pulmonary arterial systolic pressure was assessed by adding the estimated right ventricular systolic pressure to the estimated right atrial pressure (Figures 1 and 2). PASP values greater than 35mmHg were considered consistent with pulmonary hypertension.

RESULTS

Table 1: Pulmonary Arterial Hypertension and HIV Infection

Clinical Variables*	None (N = 86)	Pulm HTN (N = 5)
Demographics		
Median Age (yrs) (IQR)	38 (33, 42)	36 (34, 42)
Median nadir CD4 count (cells/uL) (IQR)	308 (167,427)	452 (301, 572)
Median current CD4 count (cells/uL) (IQR)	561 (359, 715)	623 (606, 867)
Median HIV-1 viral load (copies/ml) (IQR)	62 (25, 1510)	25 (25, 2080)
PA Pressure (mmHg) (IQR)	23 (21, 27)	36 (36, 37)
Diastolic Dysfunction (%)	31 (36%)	3 (60%)

* p = ns for all variables

Table 2: Pulmonary Artery Pressure and Clinical Variables

Variable	PA Pressure [median (IQR)]	p-value
Diastolic Function		0.15
Normal	23.0 (21.0, 26.0)	
Abnormal	26.0 (21.0, 29.0)	
PI Use		0.87
Yes	24.0 (21.0, 26.0)	
No	23.5 (21.0, 29.0)	
AIDS Risk		0.16
Low	23.0 (21.0, 27.0)	
Moderate	21.0 (20.0, 26.0)	
High	28.0 (25.0, 29.0)	
Nadir CD4		0.26
Tertile 1	24.0 (21.0, 28.0)	
Tertile 2	21.5 (19.5, 25.5)	
Tertile 3	25.5 (21.0, 29.0)	

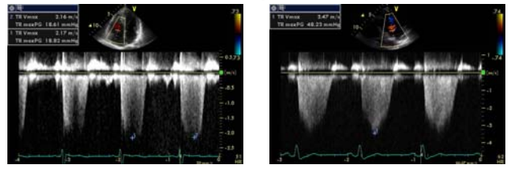
Table 3: Characteristics of Patients with Pulmonary Arterial Hypertension

Patient	Age	Sex	Race	Current CD4 (cells/uL)	Nadir CD4 (cells/uL)	Current HIV Viral Load (copies/ml)	Number of Years with HIV	PA Pressure (mmHg)	BMI	Tobacco	Hypertension	Diabetes Mellitus	Hyperlipidemia	Framingham Risk Score
1	42	Male	Caucasian	867	452	<50	9	45	25.2	No	No	No	No	1
2	36	Male	Caucasian	606	572	71,000	13	36	28.6	No	No	No	No	1
3	34	Male	Caucasian	1282	658	<50	7	37	23.6	Yes	No	No	Yes	2
4	44	Male	African American	623	167	2080	18	35	30.8	No	No	No	No	1
5	26	Male	African American	336	301	<50	31	36	22.4	No	Yes	No	Yes	1

Echocardiographic Assessment of Pulmonary Arterial Hypertension

In the absence of pulmonic stenosis, pulmonary artery systolic pressure (PASP) is estimated in echocardiography by adding the right ventricular systolic pressure (RVSP) to the right atrial pressure (RAP). RVSP is estimated by obtaining a velocity (in m/s) of regurgitant blood flow across the tricuspid valve and converting this velocity to pressure (in mmHg) via the modified Bernoulli equation [Δ Pressure = 4 x (Velocity)^2]. RAP is estimated by measuring the dimension of the inferior vena cava and assessing the change in dimension with an active sniff by the patient. If the IVC collapses completely with sniff, the RAP is estimated at 5mmHg. If the IVC collapses to less than 50% of the initial dimension, the RAP is estimated at 10mmHg. No IVC collapse with sniff indicates a RAP greater than 15mmHg. By echocardiography, PASP estimates greater than 35mmHg are consistent with pulmonary hypertension.

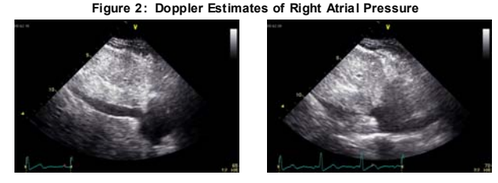
Figure 1: Doppler Estimates of Right Ventricular Systolic Pressure



Normal RVSP

Elevated RVSP (48mmg) in patient with pulmonary hypertension.

Figure 2: Doppler Estimates of Right Atrial Pressure



Normal IVC, pre-sniff

Normal IVC with sniff, estimated RA pressure 5mmHg.

DISCUSSION

- In the general population, symptomatic PAH is exceedingly rare under the age of 50 in the absence of congenital heart disease. Overall, estimates in the general population are approximately 1 in 200,000, while in AIDS patients the incidence has been estimated at about 1 in 200. Most of these estimates are in AIDS patients in the pre-HAART era.
- In this cohort of asymptomatic (median CD4 cell count > 500 cells/mm3) well controlled HIV infected pts on ART, a 5.5% rate (95% CI 1.81-12.36) of PAH was found. Our patients, who are subjected to routine drug screening, had no known intravenous drug use, which has an association with PAH, or any identifiable secondary causes of PAH. Previously, reports of an unexpectedly high prevalence of PAH in asymptomatic HIV infected patients had large numbers of intravenous drug users in their cohorts, which may be a co-founding factor and speak to their higher rates. Recently, Circalini and colleagues reported similar results of unexpectedly high numbers of HIV infected patients with elevated PSAP in a larger cohort (23 out of 510 HIV infected asymptomatic patients).
- In our pts with PAH, PAH was mild (median pressure 36 mmHg (IQR 36-37 mmHg)) and asymptomatic.
- Contrary to other studies, there was no difference with respect to CD4 and VL in pts with PAH compared to those without PAH.
- In addition, there was no association with cardiac risk factors, PI use, CD4 nadir or AIDS risk score, though this was limited by the small number of patients with PAH.
- As has been previously reported, our study population overall demonstrated a higher than expected prevalence of diastolic dysfunction (DD) (37%), which was also observed in 60% of the patients with PAH, though is was not statistically significant. While severe DD can result in PAH, the degree of DD in these pts with PAH was unlikely significant enough to contribute to PAH.

CONCLUSIONS

- This cohort of young asymptomatic well controlled HIV infected pts on ART at low risk for AIDS and cardiovascular disease had a 5.5% rate of PAH.
- No clinical variable correlated with PAH, although 60% of pts with PAH had diastolic dysfunction, this was not statistically significant.
- It is yet to be determined clearly if ART will have an influence on the incidence of PAH or demonstrate a survival benefit in HIV infected pts with PAH.
- Further prospective studies are needed to determine if these asymptomatic pts with mild PAH will progress to develop symptomatic PAH over time

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ACKNOWLEDGEMENTS

The authors would like to acknowledge the cardiac sonographers Robert Rapena, BS and Marc Marchicelli, RDCS for their assistance with this project.