Prevalence and severity of ventricular dysfunction in patients with HIV-related pulmonary arterial hypertension

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**Objectives:** To evaluate the occurrence of ventricular systolic dysfunction in human immunodeficiency virus (HIV)-related pulmonary arterial hypertension (PAH).

**Background:** Patients with HIV-related PAH may develop ventricular systolic dysfunction both as a consequence of PAH progression or of the myocardial involvement from the HIV infection itself.

**Methods:** Cardiac magnetic resonance imaging was applied to measure ejection fraction for the left ventricle and the right ventricle in patients with HIV-related PAH (n = 27) and in patients with PAH from other aetiologies (n = 115).

**Results:** In HIV-related PAH, ejection fraction values were lower and a higher proportion of patients presented with an advanced stage of ventricular dysfunction (55% vs. 25%; p = 0.009). In a multivariate model, PAH related to HIV infection remained independently associated with advanced ventricular dysfunction (p = 0.011).

**Conclusions:** Patients with HIV-related PAH have more prevalent and severe ventricular systolic dysfunction compared to patients with PAH from other aetiologies.

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PAH are more susceptible to develop ventricular dysfunction as a consequence of altered pulmonary hemodynamics has never been investigated. Of note, ventricular dysfunction has been frequently reported in the general population of HIV-infected patients.14,15 Cardiac magnetic resonance imaging (MRI) is universally accepted as the reference modality for non-invasive assessment of ventricular systolic function, with recognized advantages over other tests in terms of feasibility and reproducibility of measurements.16,17 Thus, aim of this study was to evaluate by cardiac MRI the prevalence and severity of ventricular dysfunction in PAH patients with HIV infection as compared to patients developing PAH from other aetiologies.

Materials and methods

This retrospective study was conducted in a group of 142 patients with a diagnosis of PAH, assessed between June 2003 and September 2009. As part of their screening evaluation, the enrolled patients underwent cardiac MRI and right heart catheterization, with a mean time-interval between the two tests of 14 days. The diagnosis of PAH was defined by right heart catheterization as mean pulmonary artery pressure ≥ 25 mm Hg with normal left heart filling pressures at rest (pulmonary capillary wedge pressure ≤ 15 mm Hg).18 Patients with non-PAH causes for increased pulmonary pressures (including left heart disease, lung disease, chronic thromboembolic disease) were not considered for this analysis. A group of 27 patients with normal pulmonary artery pressures and evaluated by cardiac MRI and right heart catheterization in the same period to exclude PAH was also considered for comparison.

Based on the revised WHO classification of PAH as reported in the ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension, patients with confirmed PAH were classified into different clinical subgroups: idiopathic; associated with connective tissue disorders; associated with congenital heart disease; associated with portal hypertension; associated with HIV infection; associated with drugs and toxins; and other (including thyroid disorders, glycogen storage disease, Gaucher’s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myelo-proliferative disorders, splenectomy).19 Patient with familial PAH were not included in this analysis. The Institutional Review Board approved the study and all individuals consented to the procedures.

Right heart catheterization

Right heart catheterization procedures were conducted using a Swan–Ganz catheter and standard methodology, as previously described.20 Hemodynamic measurements included: mean right atrial pressure, mean pulmonary artery pressure, systolic pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output (determined using the thermodilution method) and mixed venous oxygen saturation. Cardiac index was computed by dividing the mean cardiac output from three different measurements by the patient’s body surface area. Pulmonary vascular resistance index was subsequently calculated as the result of the following formula: (mean pulmonary artery pressure – pulmonary capillary wedge pressure)/cardiac index. Heart rate and systemic arterial pressure were recorded at the time of right heart catheterization.

Cardiac MRI

In all patients, cardiac MRI was performed on a 1.5-T magnet (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany) using a dedicated multi-element surface coil, as previously reported.21 Briefly, after the initial scout images, cine multi-phase images were obtained in the standard cardiac planes. By using long-axis images as a reference, a series of parallel short-axis images were acquired, encompassing the entire RV and LV from the base to the apex. Each cine image was obtained during a short breath-hold (8–13 s) by using a retrospective electrocardiographically gated steady-state free precession sequence (repetition time: 3.2 ms; echo time: 1.6 ms; flip angle: 60°–90°; slice thickness/gap: 8 mm/2 mm; typical matrix: 256 × 166; typical spatial resolution: 1.7 × 1.4 mm; acquired temporal resolution: 33–45 ms, based on heart rate).

MRI images were analyzed by experienced readers blinded to patient identity and using a specialized software (Argus, Siemens Medical Solutions).21 Endocardial contours were traced for the RV and the LV on each short-axis image using a semiautomated tool to obtain end-diastolic volume and end-systolic volume. For each ventricle, the stroke volume was derived from the formula: end-diastolic volume – end-systolic volume. Indexed parameters were obtained by correcting for body surface area. Ejection fraction (EF) was obtained with the following formula: stroke volume/end-diastolic volume.

By assuming that RV dysfunction typically precedes LV involvement and that the decrease in LV EF is generally mild if any in PAH patients, PAH patients were classified into different levels of progression in ventricular dysfunction: Stage 1 (initial isolated RV dysfunction); RV EF ≥ 35% and LV EF ≥ 55%; Stage 2 (advanced isolated RV dysfunction); RV EF < 35% and LV EF ≥ 55%; Stage 3 (advanced RV dysfunction combined with LV dysfunction); LV EF < 35% and LV EF < 55%. The choice of cutoffs was based on prior studies that have identified an EF equal to 55% and 50% as the lowest normal values for LV and RV, respectively.22,23 Furthermore, multiple studies have substantiated an RV EF < 35% as correlating with an increased morbidity and mortality risk in patients with chronic heart failure as well as in those with PAH.24–27 Thus, in this study RV dysfunction was considered to be “initial” with EF between 35% and 49% and “advanced” with EF < 35%.

Statistical analysis

Continuous data were expressed as mean ± SD and between-group comparisons were made with the use of Student’s t test. Discrete variables were expressed as proportion and comparisons between groups were made with the use of x^2 test. The capacity of HIV-related PAH to predict ventricular dysfunction was assessed by multivariable binary logistic analysis. Results are presented as odd ratio (OR; 95% CI) and level of significance. All statistical tests were 2-tailed and p < 0.05 was regarded as significant. SPSS (version 15.0) was used to perform the statistical analyses.

Results

In the PAH group, 27 (19%) patients had HIV infection (PAH+/HIV+), while a variety of different aetiologies could be identified in the remaining 115 patients (PAH+/HIV−), as summarized in Table 1. In details, PAH+/HIV− included 38 patients with primary idiopathic PAH, 45 patients with connective tissue disorders (25 with scleroderma, 16 with systemic lupus erythematosus and 4 with rheumatoid arthritis), 6 patients with congenital heart disease (3 with repaired atrial septal defect, 2 with repaired tetralogy of Fallot and 1 with post-Mustard operation great artery transposition), 17 patients with portal hypertension secondary to chronic liver diseases, 1 patient with anorexigen-induced PAH and, finally, 8 patients with other mechanisms underlying the development of PAH (3 with thyroid disorder, 3 with vasculitis and 2 with sickle cell disease). PAH+/HIV+ had significantly lower age and prevalence of female gender than PAH+/HIV− and patients without PAH (PAH−).
and pulmonary vascular resistance index. As well, PAH pulmonary hemodynamics, such as increased pulmonary pressures and in patients with HIV-related PAH (PAH) when compared with PAH (PAH) and with other PAH aetiologies (PAH+/HIV–).

Table 1
Demographic characteristics and invasive hemodynamic parameters in patients without PAH (PAH–) and in patients with HIV-related PAH (PAH+/HIV+) and with other PAH aetiologies (PAH+/HIV–).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAH– (n = 27)</th>
<th>PAH+/HIV– (n = 115)</th>
<th>PAH+/HIV+ (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.2 ± 13.4</td>
<td>48.3 ± 14.6</td>
<td>40.7 ± 8.8*</td>
</tr>
<tr>
<td>Female gender (n%)</td>
<td>23 (85%)</td>
<td>93 (81%)</td>
<td>18 (67%)*</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.7 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>PAH classification</td>
<td>–</td>
<td>Idiopathic (n = 38)</td>
<td>Associated with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Connective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tissue disorders</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 45)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Congenital</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 6)</td>
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<td></td>
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<td>- Portal</td>
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<td></td>
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<td>hypertension</td>
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<td>(n = 17)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Drugs and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>toxins (n = 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Other (n = 8)</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>86.2 ± 15.4</td>
<td>90.6 ± 14.7</td>
<td>86.1 ± 13.8</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71.4 ± 13.1</td>
<td>83.5 ± 15.4*</td>
<td>85.4 ± 18.2*</td>
</tr>
<tr>
<td>Systolic pulmonary arterial pressure (mm Hg)</td>
<td>29.1 ± 5.2</td>
<td>77.8 ± 20.1*</td>
<td>74.9 ± 19.1*</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>18.3 ± 3.1</td>
<td>47.9 ± 13.1*</td>
<td>48.4 ± 11.3*</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>7.9 ± 3.3</td>
<td>10.6 ± 5.2*</td>
<td>10.1 ± 3.9</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>1.7 ± 3.0</td>
<td>9.2 ± 6.0*</td>
<td>12.9 ± 9.6*</td>
</tr>
<tr>
<td>Pulmonary vascular resistance index (Wood units m²)</td>
<td>3.0 ± 1.0</td>
<td>13.3 ± 7.4*</td>
<td>14.8 ± 7.4*</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>72.0 ± 5.0</td>
<td>63.0 ± 10.2*</td>
<td>55.4 ± 13.3*</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>4.0 ± 1.1</td>
<td>3.3 ± 1.2*</td>
<td>2.9 ± 0.9*</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. PAH–; *p < 0.05 vs. PAH+/HIV–.

When compared with PAH–, patients in both PAH+/HIV+ and PAH+/HIV– groups showed similar levels of compromised pulmonary hemodynamics, such as increased pulmonary pressures and pulmonary vascular resistance index. As well, PAH+/HIV+ and PAH+/HIV– patients both had increased RV volumes and a tendency toward reduced LV volumes (Table 2).

Compared with PAH+/HIV–, PAH+/HIV+ patients showed lower values of RV EF (28.6 ± 11.4% vs. 35.8 ± 12.3%, respectively; p = 0.006) and LV EF (51.3 ± 11.2% vs. 58.4 ± 10.8%, respectively; p = 0.01; Fig. 1). Various degrees of ventricular dysfunction could be observed in the global population of PAH patients, with 67 patients in Stage 1, 32 patients in Stage 2 and 44 patients in Stage 3. A larger proportion of patients in the PAH+/HIV+ group than in the PAH+/HIV– group presented a Stage 3 of ventricular dysfunction (55% vs. 25%, respectively; p = 0.009; Fig. 2).

Association between HIV-related PAH and ventricular dysfunction was confirmed by the increasing prevalence of HIV+ patients going from Stage 1 (10%) to Stage 2 (22%) and Stage 3 (32%; p = 0.09; Fig. 3). In a multivariable binary logistic regression analysis including age, female gender and mean pulmonary arterial pressure as covariates, PAH related to HIV infection was identified as a significant predictor of Stage 3 ventricular dysfunction (OR = 1.065; 95% CI, 1.044–1.086; p = 0.011).

Discussion

This study evaluated the prevalence and severity of ventricular dysfunction as detected by cardiac MRI in patients with HIV-related PAH compared with other subtypes of PAH. The results demonstrate that, compared with patients with a diagnosis of PAH from other aetiologies, in HIV-related PAH ventricular systolic dysfunction is more frequently observed and with more advanced degrees of severity. The two groups were similar in terms of pulmonary hemodynamic impairment.

PAH prevalence in HIV-infected patients is much higher than what is reported in the general population and patients with HIV are considered as a separate subgroup in clinical PAH classification. Currently, guidelines suggest for HIV-related PAH similar treatment strategies as for other PAH patients, even though a small number of randomized controlled trials have actually included patients with HIV infection.

The development and progression of PAH did not show any relation with the stage of underlying HIV disease and degree of immunodeficiency. However, detection of PAH has been recognized as a strong independent predictor of death in HIV-infected patients at any stage of the disease. The majority of patients with HIV-related PAH die of complications of PAH rather than HIV infection itself. As well, some reports evaluating general PAH populations indicated that survival may be worse in patients with HIV infection compared with other clinical subgroups of PAH. In prognostic studies evaluating patients with HIV-related PAH, right heart failure could be recognized as the underlying cause for the majority of the reported deaths. The use of highly active antiretroviral therapy significantly increased the overall survival in HIV-infected patients. However, the diffuse use of these drugs apparently does not prevent the development of PAH in HIV-infected patients and, in those already with PAH, no improvement in hemodynamic parameters is generally detected.

The pathophysiological mechanisms underlying the development of PAH in patients with HIV infection are poorly understood. When considering the pathological abnormalities detected in the small pulmonary arteries, characterized by intimal, medial and adventitial proliferation and hypertrophy, endothelial dysfunction and development of plexiform lesions, HIV-related PAH did not significantly differ from the other subtypes of PAH. Apparently, HIV does not directly infect vascular endothelial cells or smooth muscle cells. However, complex interactions between HIV proteins and host cells may induce a chronic inflammatory state with immune activation. Persisting exposure of lung endothelial cells...
to viral proteins by inducing increased release of proinflammatory cytokines and growth factors has been hypothesized as one of the most important mechanisms for lung vascular injury in patients infected with HIV.\textsuperscript{35}

In patients with PAH, afterload mismatch is the first trigger as well as the main determinant of ventricular dysfunction, but ischemia, inflammation and an abnormal activation of neurohormonal signaling may also be involved in its progression.\textsuperscript{36,37} Individual differences in the capacity to activate the adaptive mechanisms to pressure overload may in part explain the observed variability in the progression of ventricular dysfunction.\textsuperscript{38} Of relevance, ventricular response to increased afterload is an important determinant of patient outcome in PAH.\textsuperscript{11} It has been suggested that a PAH treatment strategy guided by repeated assessment of ventricular function may be superior to the traditionally applied treatment algorithms, but this hypothesis has not been proven yet.\textsuperscript{38}

Ventricular function has been identified as a significant predictor of survival in different subgroups of PAH, including patients with HIV infection.\textsuperscript{32,40,41} The present study involves a population of patients with PAH from different aetiologies and shows more advanced levels of ventricular dysfunction in those with HIV infection. Ventricular dysfunction is not an uncommon finding in the general population of HIV-infected patients.\textsuperscript{14,15} During a 4-year follow-up of 296 HIV-infected patients recruited in the era preceding the introduction of highly active antiretroviral therapy, Currie et al showed that both RV dysfunction and LV dysfunction may develop in about 5% of patients.\textsuperscript{42} Several mechanisms can potentially be involved in the observed higher ventricular sensitivity to altered pulmonary hemodynamics, including direct HIV myocardial infection,\textsuperscript{43} autoimmune response to myocardial infection,\textsuperscript{44} nutritional deficiency with erosion of lean body mass,\textsuperscript{45} and prolonged effects of therapy.\textsuperscript{46} In this regard, experimental studies investigating HIV-related cardiomyopathy and using transgenic rat models expressing several HIV-1-related proteins documented a direct negative effects of HIV proteins on cardiac myocytes, independent of viral infection or replication.\textsuperscript{47,48} However, in support of an indirect role of the virus in promoting cardiac damage other studies showed that HIV effectively enters, but does not replicate in cultured ventricular myocytes.\textsuperscript{49}
Study limitations

The reported findings should be evaluated by taking into account that some of the PAH clinical subgroups (e.g. patients with congenital heart disease) were poorly represented or absent (e.g. patients with familial PAH) in the study population. Some of the vasoactive drugs employed in PAH patients proved to be effective in reversing adverse ventricular remodeling, but therapy was not a controlled variable in this study.50 Regarding treatments for HIV infection, the time of enrollment for all patients with HIV-related PAH included in this study was largely after the advent of highly active antiretroviral therapy. The recruited patients have been screened to exclude ischemic heart disease, although coronary angiography was not always performed. Study findings may have been partially influenced by the fact that cardiac MRI and right heart catheterization were not done on the same day and hemodynamic changes may have occurred in some patients during that time-interval. Same-day evaluation was obtained in 75 (33%) patients and clinical, cardiac MRI and right heart catheterization characteristics of these patients, overall, did not differ from those of the other patients (data not shown).

Conclusions

In conclusion, considering patients with PAH from different aetiologies, those with HIV-related disease showed higher prevalence of ventricular dysfunction. HIV-related PAH appears to be significantly correlated with more advanced stages of ventricular dysfunction.

Whether the higher susceptibility of patients with HIV-related PAH to develop ventricular dysfunction may be responsible, at least in part, of the worse prognosis reported in this compared to other PAH subgroups needs to be verified in appropriate studies.11,10 Current guidelines for the management of PAH do not prescribe specific monitoring or treatment strategies for patients with HIV.11,10 However, the findings of the present study suggest more caution in planning the schedule for repeated cardiovascular assessment in HIV-related PAH.

Measuring EF by cardiac MRI is a precise and reproducible method to quantify global ventricular function. Alternative methods, such as strain and strain rate measurements by echocardiography or cardiac MRI, allow the quantification of regional ventricular function. These methodologies may suffer of limitations in terms of feasibility and standardization, but showed promise for early identification of ventricular dysfunction.31 Unfortunately, many of the protective pharmacological strategies limiting the impairment in ventricular function may be less effective in patients with PAH, particularly when the treatment is started in patients already with ventricular dysfunction.25 Future research should evaluate whether new anti-HIV treatments can prevent or modulate in these patients the occurrence of PAH, together with the efficacy of specific agent to prevent the development of ventricular dysfunction in PAH.

References


