RIGHT VENTRICULAR FUNCTION IN A SIMIAN IMMUNODEFICIENCY VIRUS MODEL OF EARLY PULMONARY HYPERTENSION

Authors: Ian Christman¹,², Rebecca R. Vanderpool¹, Rebecca A. Tarantelli¹, Karen Norris³, Marc A. Simon¹,²
Author’s Affiliations: ¹Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute, ²Department of Bioengineering, ³Department of Immunology, University of Pittsburgh

INTRODUCTION
Pulmonary Arterial Hypertension (PAH) is defined as an increase in pressure in the pulmonary artery (PA) and results in right ventricular (RV) failure due to progressive vascular remodeling. One etiology of PAH is the Human Immunodeficiency Virus (HIV) with a prevalence of 0.5 to 2%, which may also cause isolated RV dysfunction [3]. Patients with HIV-PAH have a 40% 2 year mortality rate [1]. The effects of HIV-PAH on RV function as the disease progresses are currently unknown. To study the progression, a unique animal model of HIV-PAH was developed by Dr. Karen Norris’ lab. [1] The Simon lab has been collaborating with the Norris lab to study RV function. This model has been shown to develop pulmonary vascular disease similar to human PAH. In particular, this model provides a unique opportunity to study the early development of RV dysfunction as the disease develops through measuring pulmonary artery blood flow and RV pressure parameters.

In the model, 22 rhesus macaques were infected with the Simian Immunodeficiency Virus (SIV). After infection, they underwent right heart catheterizations every 3 months for a 10-12 month period to measure RV pressure. Echocardiographic images were taken concurrently to measure PA blood flow. RV function and RV-pulmonary arterial coupling can be quantified from RV pressure and flow [2] and provide a detailed physiological understanding of the development of RV dysfunction and the pathogenesis of HIV-PAH in this highly characterized model [1].

OBJECTIVE
The objective of the project was to utilize MATLAB to measure PA blood flow and RV pressure parameters over time in SIV-infected monkeys. The calculated parameters would then be used to quantify RV function and pulmonary resistance through RV pressure and PA flow coupling as HIV-PAH progresses. Statistics will be used to compare groups that exhibit PAH to those that don’t to understand better the progression of PAH, specifically what parameters change over time in association with PAH.

HYPOTHESIS/SUCCESS CRITERIA
For the results to be considered valid, the MATLAB codes must output physiologically correct data for rhesus macaques. For Cardiac output calculations, they must be in a physiologic acceptable range of around 20-35 mL/s. Pressure data must exhibit a systolic RV pressure in a range of 20-50 mmHg.

RV dysfunction will occur with an increase in max dP/dt, a measure of force of RV contraction during systole, in PAH positive animals compared to PAH negative animals over time. Diastolic dysfunction will also be present if there is a decrease in min dP/dt, a measure for relaxation time, in PAH positive animals compared to PAH negative animals over time. RV function will be uncoupled from its pulmonary vascular load with an increase in total pulmonary vascular resistance index (measure of pulmonary artery’s resistance to blood flow from RV) in PAH positive animals compared to PAH negative animals over time.

METHOD
From right heart catheterization, the SIV-infected rhesus macaques were categorized in three groups. The PH negative group was defined as animals who’s mean PA pressure (mPAP) did not exceed 25 mmHg. The PH positive progressive group was defined as animals who’s mPAP increased over 25 mmHg and staid above. The PH positive transient group was defined as animals who’s mPAP increased above 25 mmHg then decreased below.

To measure PA flow parameters, stored echocardiographic images (image of blood velocity over time in PA) were traced and digitized using a custom MATLAB program. A MATLAB program was then created to interpolate the digitized data at 1000 Hz and allow for manual point selection. For each beat, the flow velocity start time and flow velocity end point were selected. Between flow velocity start to flow velocity end for each beat, the stroke volume was calculated by calculating the velocity time integral and multiplying by the baseline x-ray computed tomography derived PA cross sectional area. The stroke volume was then averaged for 3 to 4 beats. Heart rate was calculated by averaging the time from flow velocity start between successive beats. Cardiac output was calculated by multiplying average stroke volume by average heart rate. Cardiac index was obtained by dividing cardiac output by BMI for each animal to adjust for varying sizes. To measure RV pressure parameters, RV pressure data from the right heart catheterization was digitized to a text file. A MATLAB program was created to create pressure waves from the digitized pressure data. A custom MATLAB program then

![Figure 1. Doppler data (A) is traced and interpolated (B). Point selection schematic (C).](image-url)
imported the pressure waves for each animal. For each time point, 3 to 4 beats were averaged into one pressure wave. The wave was then aligned with a sinusoid. The program then calculated systolic RV pressure (sRVP), max dP/dt, end diastolic pressure (EDP), and min dP/dt. To measure total pulmonary vascular resistance index (TPVRI), mean PA pressure was divided by average cardiac index for each animal at every time point.

Parameters were compared between the PH negative group and the PH positive progressive and PH positive transient groups at baseline, 6months post infection, and terminal (10-12 months post infection). The parameters were statistically through PRISM using the Kruskal-Wallis test with a Dunn test for multiple comparisons at each time point due to the non-linear nature of the data.

RESULTS

At 6 months post infection (6mpi), systolic RV pressure was elevated in transient PH (P=0.005). At 9-12mpi, sRVP was elevated in progressive PH (P=0.006). At 6mpi and 9-12mpi, there were no differences in cardiac index and flow despite early increases in RV pressure. At 6mpi, max dP/dt was elevated in transient PH (P=0.002). At 9-12mpi, max dP/dt was elevated in the progressive PH group (P=0.02). TPRVI had no significant differences between groups at 6mpi and 9-12 mpi. During diastole, end diastolic pressure (EDP) was elevated at 6mpi in transient PH (P=0.005). Min dP/dt decreased in progressive PH at 9-12 mpi (P=0.02).

A limitation to the project was the short time span of the study. PAH in the rhesus macaques was studied for 10-12 months. In humans, PAH progresses for longer time periods. The discovery of RV diastolic dysfunction in the early form of PAH was unique and future research will analyze the diastolic dysfunction. Future research will also study the relationship between biological markers (i.e. collagen number) in the right heart and changing parameters.

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REFERENCES

