CLASSIFICATION OF PULMONARY HYPERTENSION BY SHAPE ANALYSIS OF THE HUMAN RIGHT VENTRICLE: ROBUSTNESS AND PRELIMINARY ASSOCIATION WITH CLINICAL OUTCOMES

Eleanor L. Desmond[1], Jing Xu[2], Timothy C. Wong[3], Marc A. Simon[3], Stefano Giani[1], and John C. Brigham[1,2]

[1] Durham University, Department of Engineering, Durham DH1 3LE, United Kingdom, {eleanor.desmond, stefano.giani, john.brigham}@durham.ac.uk

[2] Department of Civil and Environmental Engineering, University of Pittsburgh, Pittsburgh PA 15261, USA, jix57@pitt.edu

[3] Cardiovascular Institute, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15261, USA, {wongtc, simonma}@upmc.edu

SUMMARY

Pulmonary hypertension is a progressive disease that affects the shape and function of the right ventricle (RV). This study uses 3D statistical shape analysis of cardiac imaging data to uniquely examine the function of the RV by analysing relative shape change in hypertensive patients. The non-invasive approach is anatomically consistent and may provide new metrics for the diagnosis of cardiovascular diseases. Preliminary data shows an association between two modes of RV shape and patient outcomes. Important work is now underway to establish the robustness of the method and to increase automation; both critical to integrating shape analysis in a clinical setting.

Key words: *right ventricle, pulmonary hypertension, shape analysis*

1 INTRODUCTION

Pulmonary Hypertension (PH) is a progressive cardio-pulmonary disease that has been observed to significantly affect the shape, mechanical properties, and overall mechanical function of the heart. PH describes high blood pressure in the arteries of the lungs from any cause, and is defined as a mean pulmonary arterial pressure of above 25mmHg at rest as assessed by, right heart catheterization [1]. The non-specificity of early PH symptoms leads to a tendency for PH to be confused with other, less serious conditions and can delay diagnosis. This non-specificity, in conjunction with the disease's debilitating and progressive nature is extremely detrimental to long-term patient outcomes. In particular, the median survival time after diagnosis for untreated pulmonary arterial hypertension (PAH) is 2.8 years [2].

The right ventricle (RV) is particularly affected by PH due to the direct link to the pressure overload. The RV in PH experiences shape and mechanical function changes under the sustained pressure overload to a higher degree than the rest of the heart in many instances, and the ability of individual right ventricles to adapt is a major determinant of prognosis and survival [3][4][5]. Despite the presence of a clear correlation between RV shape and both function and disease progression, there is still no clear understanding as to why certain patients maintain near-normal cardiac outputs for many years despite experiencing severe PH, yet other, apparently healthier patients experience dramatic and rapid deterioration, leading to RV failure [2]. Thus, attributing a causal link between ventricle shape and hypertensive state would be a significant contribution to diagnosis and treatment of this deadly disease. The present study is aimed at generating this link between the shape of the human RV and the state of PH. The following details the clinical dataset

examined and the statistical shape analysis methodology used to analyze that dataset, which is followed by the discussion of the current results relating shape to the state of PH (including outcomes) and potential future research directions.

A shape analysis framework based on harmonic mapping has been developed in [2] that produces unique mathematical representations of 3D closed surfaces. This method requires minimal referential data, is anatomically consistent and is not reliant on mesh uniformity or conformity.

2 METHODOLOGY

3.1 Clinical Data Acquisition

The dataset used was composed of clinically-obtained, cardiovascular magnetic resonance (CMR) images from patients who underwent both CMR and right heart catheterization. Images were acquired using a 1.5-Tesla Siemens Magnetom Espree machine equipped with a 32-channel cardiac coil. Standard breath-held cine imaging was acquired with steady-state free precession in the short axis orientation, spanning base to apex. Image stacks were taken in 6mm thick slices, skipping 4mm in between. Typical imaging parameters included 30 phases per R-R interval, matrix 256 by ~144, flip angle 51 deg, TE 1.11 ms, acceleration factor 3.

A total of 50 patients were considered, with 33 of these patients assessed as having pulmonary hypertension and 17 as non-hypertensive. Images were extracted at two distinct cardiac phases for each patient; end-systole and end-diastole, to create 100 total RV shapes to analyze. All patients included within the study are symptomatic, and therefore, the non-hypertensive individuals are not representative of the typical healthy ventricle. Figure 1 shows the pulmonary arterial pressure and pulmonary capillary wedge pressure for each of the 50 patients in the dataset. The distribution of pressure is quite broad, including several patients on the border of being classified as hypertensive or not. Patients are classified as Type 1 PH or Type 2 PH in this case based on the pulmonary capillary wedge pressure, which is an indirect measure of left atrial pressure.
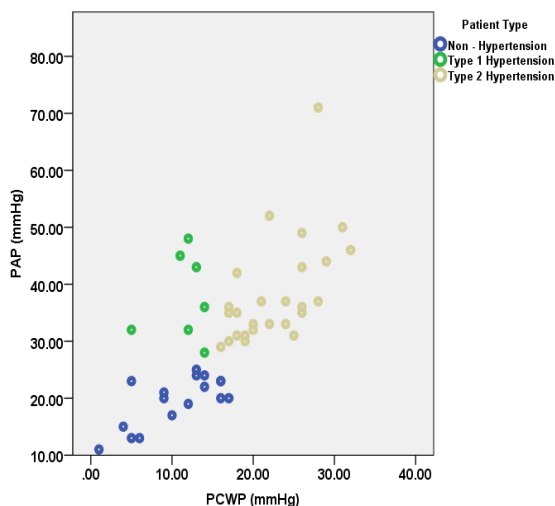

Figure 1: Pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PWCP) for each patient in the dataset.

2.2 Three-Dimensional Statistical Shape Analysis

The statistical shape analysis strategy employed is a unique approach for anatomically consistent assessment of shape variations in three-dimensional (3D) closed surface representations of anatomical structures that was developed by the authors [2]. This approach involves five steps following the acquisition of the medical images:

1. Segment the image stacks to obtain 3D surfaces (i.e., point clouds) of the RV at the desired phases in the cardiac cycle for all patients.

2. Smooth the surfaces of the RV using a standard Gaussian filter and convert the surfaces into 3D closed surface meshes suitable for numerical analysis (e.g., finite element meshes).
3. Topologically map (i.e., parameterize) every 3D mesh to a unit sphere through a harmonic mapping approach to create a unique shape function for each 3D shape.
4. Apply the proper orthogonal decomposition (POD) method to the complete set of shape functions to determine and rank a set of shape features (i.e., modes and corresponding coefficients from decomposition).
5. Utilize the modal coefficients to determine which shape features are significant (as relating to features of the disease) to the patient population and/or create classifiers to predict disease classification from these coefficients, etc.

Of particular importance is that the harmonic mapping step (Step 3) requires 2 anatomical reference points (referred to as poles) and an anatomical reference line (referred to as the dateline). For the analysis herein the anterior border between the free wall and septum of the RV with endpoints at the intersection with the pulmonary valve and apex was used as the dateline, and the intersection points were the poles. As noted, the MRI image stacks were segmented to obtain 3D surfaces of the RV at end-systole and end-diastole, and all segmentation was overseen by a trained cardiologist.

3 RESULTS AND CONCLUSIONS

After applying the statistical shape analysis strategy to the 50 patient set, correlation between each modal coefficient across the population and a variety of hemodynamic measures (including pulmonary arterial pressure and pulmonary capillary wedge pressure, among others) was assessed. Two modes of the RV shape were identified as being more significantly correlated to the hemodynamic variables than the others. These were Mode 8 and Mode 13 (note that the mode number relates to rank of the associated eigenvalue, ordering from highest eigenvalue to lowest). These two modes are visualized in Figure 2, which shows each mode's effect on the mean shape of the RV from the patient set.
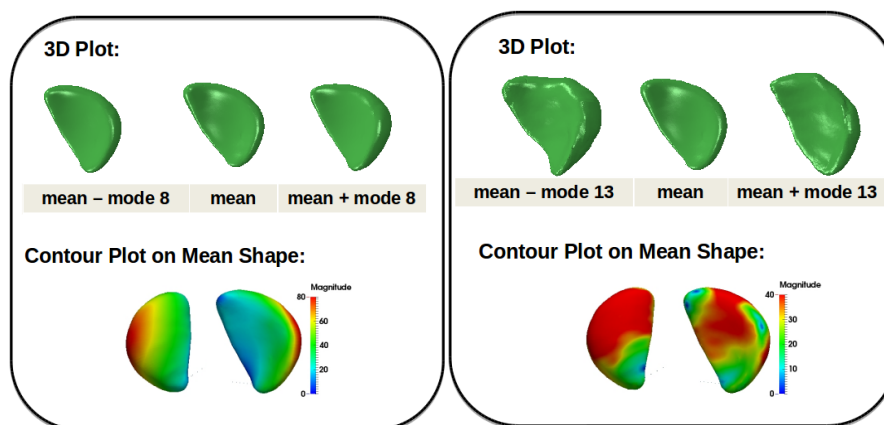

Figure 2: Mode 8 (left) and Mode 13 (right) obtained from the statistical shape analysis, shown in terms of their effect on the mean RV shape (colour contours are shape change magnitude).

It is particularly interesting is to see that the two modes have specific and clear effect on the RV shape. Mode 8 appears to relate to an expansion or contraction of the RV free wall. More significantly, Mode 8 was seen to positively associate with PH, in that a larger value of the Mode 8 coefficient (meaning a bigger RV free wall) corresponded to higher pressures. Alternatively, Mode 13 appears to relate to a change in curvature of the septum and was negatively correlated with the pulmonary arterial pressure. A relationship between septal curvature and PH has been observed before, but this is the first time a 3D statistical shape analysis approach has so clearly quantified this relationship. The results showed that a positive value of the Mode 13 coefficient increased the "flatness" of the septum, which is commonly observed to be a less healthy state, and this was significantly correlated to the increase in pulmonary arterial pressure.

The coefficients of Mode 13 were then hypothesized to be significantly correlated to the state of PH. So, the value of the Mode 13 coefficients were considered with respect to patient outcomes, as defined as death or hospitalization with heart failure within 5 years of the image acquisition. Figure 3 shows the value of the Mode 13 coefficient for each of the two outcomes.
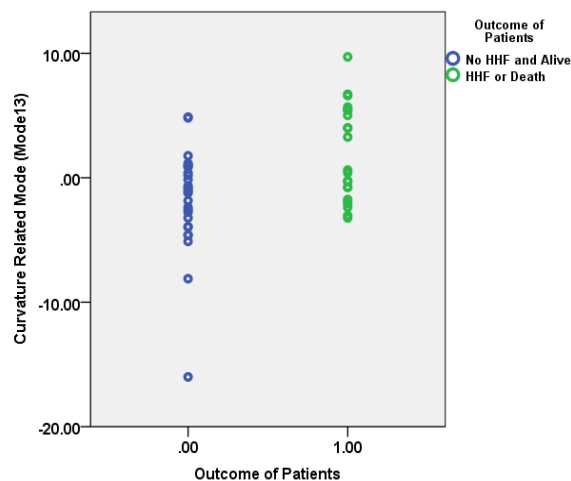

Figure 3: Curvature mode, Mode 13, coefficients for each of the 50 patients divided by outcome as either dead/hospitalized with heart failure (HHF) or not.

Although the correlation between outcomes and the Mode 13 coefficient is not perfect, there is clearly a division between the two groups that is related to the value of the modal coefficient. Moreover, the division between the two groups is significantly clearly for this Mode 13 coefficient than any other measure available from the dataset, including all hemodynamic measures that were clinically available. This correlation was significant even when adjusting for patient age. Thus, there is significant evidence to motivate further evaluation of the relationship between shape of the RV (as quantified by statistical shape analysis) and the state of PH. Important work is now underway to evaluate the robustness of the method, which is critical to clinical integration, and to explore how the technique can be automated to improve accuracy and minimise error associated with human interference.

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