Right Ventricular Function Is Delimited By Oxygen Metabolism During Pulmonary Hypertension

Submitted in partial fulfillment of the requirements for
the degree of
Master of Science
in
Biomedical Engineering

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B.E., Biomedical Engineering, Stony Brook University

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December 2014
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ABSTRACT

Background: The severity of symptoms and survival in patients with idiopathic pulmonary artery hypertension (IPAH) is closely related to right ventricular function (RV). Unfortunately, knowledge of the role of the RV in health and disease has lagged behind that of the LV and there is a need to develop methods to predict RV dysfunction in IPAH.

Methods: A biomechanical metabolic model of RV function was evaluated using data taken from patients (n=15) with IPAH. The model assumed that RV O$_2$ supply (determined using PET data) and RV O$_2$ demand (determined from the hemodynamic state of the RV) were equal. This model was first verified and then used to suggest an index of RV dysfunction in IPAH.

Results: The model showed that there was a linear positive correlation ($R^2=0.68$) between RV total mechanical power output (J/s) and O$_2$ consumption (mL/s) (RV total power = 21.03*O$_2$ consumption +0.6) even under pathological conditions, which closely matches the theoretical value of 21J/mL. Patients with the highest RV O$_2$ supply exhibited low mechanical efficiency ($E_M$) despite their high RV total power output. These findings confirm that under high afterloads, majority of RV energy (78%) is spent performing pressure (internal) rather than volume (external) work. The model was able to predict cardiac output for majority of the patients (66%), however there was a large error in the predicted CO of the remaining patients (33%).

Conclusion: This biomechanical metabolic model could be a useful clinical tool for analyzing the extent of increased RV loading and how well a patient has accommodated by increasing oxygen supply.
CHAPTER 1
INTRODUCTION

1.1 Idiopathic Pulmonary Arterial Hypertension

Idiopathic pulmonary arterial hypertension (IPAH) is characterized by a progressive increase in pulmonary artery pressure beyond 25 mmHg \(^8\) and is associated with a high risk of morbidity and mortality. IPAH is twice as common in women than in men and generally affects young individuals \(^{10}\). The initial symptoms of IPAH, such as shortness of breath and fatigue, are common to many other diseases often resulting in a delayed diagnosis until more severe symptoms (such as chest pain, heart palpitations, and fatigue) arise \(^9\). Therefore it is possible for a patient to have IPAH for several years before being diagnosed with an advanced and life-threatening form of the disease. The average age for diagnosis of IPAH is 36 years with a 50% chance of three-year survival post-diagnosis \(^{10}\) and a five-year survival rate of only 34% \(^{10}\).

1.2 Right Ventricular Pathophysiology In IPAH

RV function is the most important determinant of IPAH severity and patient survival, however there is a lack of agreement on how to clinically assess RV function/failure in the medical community \(^{12}\)[13][14]. The pathophysiology of RV function under high afterloads is poorly understood. IPAH results in an increased workload for the right ventricle (RV) and consequently an increased myocardial oxygen demand \(^4\).

![Diagram](image)

**Figure 1.** RV vs. LV Pressure Volume Loop
As opposed to the left ventricle (LV), the RV primarily performs more volume work (defined as the work required to generate blood flow during ejection) than pressure work (defined as the work required to pressurize blood during isovolumic contraction) as can clearly be seen by the triangular shape of the RV Pressure-Volume Loop (Fig. 1). Compared to the LV, the RV spends little time performing isovolumic contraction as it is required to pump against a low pulmonary resistance and is often unable to sustain high pressure pumping against an increased workload, eventually leading to RV failure and death \cite{15}. Several studies have speculated that the delayed opening of the pulmonic valve under high afterloads results in prolonged isovolumic contraction, which comes at the cost of a higher myocardial oxygen demand to perform a larger amount of pressure work \cite{15}. In this situation, the RV expends a large amount of energy to pressurize the blood but is unable to generate the energy necessary to eject blood out of the ventricle and maintain stroke volume. In addition to prolonged isovolumic contraction, the highly compliant RV dilates to accommodate stroke volume thereby increasing myocardial wall stress, which further drives an increased oxygen demand \cite{15}. In response to the increasing myocardial wall stress, the RV compensates by remodeling into a hypertrophied state so as to generate high ejection pressures and maintain stroke volume \cite{16}. As IPAH progresses and the afterload increases, RV ejection fraction decreases and eventually causes systemic hypotension. Systemic hypotension results in a decreased right coronary artery perfusion and eventually there comes a point when the myocardial oxygen demand cannot be met by the supply and the RV becomes ischemic and fails \cite{15,16}. Studies have shown that in increasing myocardial oxygen demand can be met either by increasing right coronary artery flow or by increasing myocardial oxygen extraction fraction (OEF) \cite{1,4}. Experiments in open-chest dogs have demonstrated that under a sustained high afterload, right coronary artery hyper-perfusion can reverse systemic hypotension
and RV failure\textsuperscript{17,18} by augmenting oxygen supply. Oxygen extraction fraction is the percentage of oxygen removed from the blood by tissue as it passes through the network of capillaries\textsuperscript{4}. A recent clinical study showed that PAH patients that exhibited a OEF had a lower exercise-induced RV mean blood flow and cardiac output compared to patients with a low OEF\textsuperscript{20}. Although the cellular mechanisms that underlie decreased myocardial oxygen and their relationship to RV function under high afterload have not been directly studied, the myocardial oxygen supply-demand relationship is an extremely critical determinant of RV mechanical performance under high afterloads.

1.3 Clinical Assessment of RV Function/Failure in IPAH

The clinical gold standard for identifying RV dysfunction is by measuring RV hemodynamics (pulmonary artery pressure, RV systolic and/or diastolic pressure, RV ejection fraction, and heart rate) and is achieved through invasive right heart catherization procedures\textsuperscript{21}. Although this method serves as a good diagnostic tool, it provides little to no insight into the interaction between oxygen metabolism and RV mechanical performance and therefore this method is not capable of predicting a patient’s ability to compensate should the afterload further increase. Additionally, this procedure can be too dangerous to perform in critically ill patients and can cause pulmonary artery rupture, pneumothorax, and in some cases, infection\textsuperscript{21}. Another clinical tool for the diagnosis of RV dysfunction is echocardiography\textsuperscript{15}. Echocardiography allows for RV visualization and identification of a hypertrophied, dilated, or poorly contractile RV and the associated possible causes\textsuperscript{15}. Promising quantitative measures of RV function include: (1) Tricuspid Annular Systolic Velocity (2) Myocardial Performance Index and (3) Tricuspid Annular Plane Systolic Excursion\textsuperscript{22}. Unfortunately, these quantitative measures are highly load-dependent and therefore have little to no predictive value. Echocardiography can
also be used to estimate PA and RV pressures and RV volume, however, these measurements are not as accurate as those obtained via catheterization or cardiac MRI\textsuperscript{[22]}. This method is also used to obtain RV structural information including RV volume. However due to the complex geometry of the RV, this method requires multiple tomographic views to perform a complete appraisal of RV structure and function\textsuperscript{[21]}. 

There is no single parameter that is capable of predicting RV failure. Therefore, several mathematical models that describe the relationship between ventricular mechanical work and myocardial oxygen supply have been developed\textsuperscript{[1][21]}. For example, Wong et al\textsuperscript{[4]} developed a model that calculated RV mechanical efficiency in terms of RV stroke power and RV oxygen consumption but failed to acknowledge RV isovolumic power and were therefore unable to explain inefficiencies\textsuperscript{[4]}. To provide a global picture of RV function, mathematical models are often highly complex and do not provide the user with an intuitive understanding of the model and are thus less likely to have clinical applications. Furthermore, many existing mathematical models rely on calculations of wall tension and stress indices (preload, afterload, and contractility) that are highly dependent on geometric assumptions of the RV thereby introducing a high degree of variability. Therefore a simple analytical model that provides an effective predictive index of RV function/failure based on the RV mechanical-metabolic relationship is necessary.

1.4 Hypothesis

The purpose of this work was to evaluate the accuracy and clinical application of a novel biomechanical metabolic model of RV function. This model was developed based on the hypothesis that the ability of the RV to perform mechanical work under a high afterload is dependent on its oxygen supply. Clinical data from patients suffering from idiopathic pulmonary hypertension (n=15) was used to validate this model.
CHAPTER 2
MODEL AND METHODS

2.1 Biomechanical Metabolic Model of Right Ventricular Function

This model is based on the concept that at equilibrium RV oxygen consumption must be equal to oxygen supply as anaerobic metabolism is unable to sustain ventricular power generation for a long period of time. We hypothesized that if the myocardial oxygen demand under a specific afterload is greater than the maximum oxygen supply (assuming that the right coronary artery is maximally dilated), the RV will be forced to reduce its power output in order to re-equilibrate oxygen demand with supply. Therefore, in the absence of ischemia, myocardial oxygen demand will be reflected by the rate of myocardial oxygen consumption. We have adapted the virtual work model for the LV from Elbeery et al. \(^{[1]}\) to express RV oxygen consumption as an energy equivalent of RV work. Using this model, the rate of ventricular oxygen consumption (mL/min) is linearly related to the total mechanical power expenditure (\(P_T, \text{J/min}\)) of the right ventricle by a factor of 0.0495:

\[
\text{O}_2 \text{ consumption (mL/min)} = 0.0495 \times P_T 
\]  
(1)

In the case of the RV, the total mechanical power (\(P_T\)) generated includes the rate at which internal work is performed to increase RV pressure during isovolumic contraction (isovolumic power, \(P_I\)) and the rate at which external work is performed to create blood flow during ejection (stroke power, \(P_S\)).

\[
P_T = \frac{HR(p_{rv,ej} - p_{rv,ed})V_{ed}}{T} + \frac{1}{T} \int_0^T Q p_{pd} p_{pe} \, dt 
\]  
(2)

In which HR is the heart rate, \(p_{rv,ej}\) is the average RV ejection pressure, \(p_{rv,ed}\) is the average RV end-diastolic pressure, \(V_{ed}\) is the RV end-diastolic volume, \(T\) is the period under consideration,
\( Q_{pa} \) is the instantaneous pulmonary artery flow, and \( p_{pa} \) is the instantaneous pulmonary artery pressure.

In order to simplify Eq. (2) we represent it in terms of RV mechanical efficiency and afterload where mechanical efficiency (\( E_M \)) is the ratio of useful stroke power (\( P_S \)) to the total power generated by the RV (\( P_T \))

\[
E_M = \frac{P_S}{P_T} \quad \text{or} \quad P_T = \frac{P_S}{E_M}
\]  

(3)

Substituting \( P_T \) from Eq. (3) into Eq. (1) we get

\[
O_2 \text{ consumption (mL/min)} = 0.0495 \frac{P_S}{E_M}
\]

(4)

Due to the lack of instantaneous pulmonary artery flow data, we used two different methods to calculate stroke power. The first method utilized a flow profile simulation algorithm based on the following piecewise function:

\[
Q(t) = \begin{cases} 
A(SV)(e^{\alpha t})\sin\left(\frac{\pi t}{t_{es}}\right) & 0 < t < t_{es} + 0.02 \\
Q(t_{es} + 0.02)\left[1 - \frac{t - t_{es} - 0.02}{0.02}\right] & t_{es} + 0.02 < t < t_{es} + 0.04 \\
0 & t_{es} + 0.04 < t < t_{ed}
\end{cases}
\]

(5)

Where \( A \) is an amplitude proportionality factor, \( SV \) is the stroke volume, \( t_{es} \) is the time at which RV ejection ends, \( t_{ed} \) is the time at which RV diastole ends, and 0.04s is assumed to be the duration of pulmonary valve regurgitation. The value of the amplitude proportionality factor \( A \) was determined by the condition that mean \( Q(t) \) had to be equivalent to the CO. Finally, the invented flow (\( Q_i(t) \)) and discrete pulmonary artery pressure data for the first 5 sequential heartbeats that were complete and that corresponded to each RV ejection interval were
multiplied and integrated using the trapezoidal method to calculate stroke work (as in Eq. 2). The stroke work for each heartbeat was divided by the period of integration \( T \) to obtain beat-by-beat stroke power. Finally, the mean stroke power was calculated by averaging the stroke power for the same 5 heartbeats for each patient.

The second method approximated PA flow as being steady and equivalent to the cardiac output at all times. Therefore, using only the zeroth harmonic, stroke power was approximately equal to the product of mean pulmonary artery pressure \( \bar{p}_{pa} \) and CO. Thus:

\[
O_2 \text{ consumption (mL/min)} = 0.0495 \frac{\bar{p}_{pa}CO}{E_M} 
\]  

We assume that myocardial oxygen consumption is equal to the oxygen supply:

\[
O_2 \text{ supply (mL/min)} = 1.34 fQ_{cara}S_{a1}C_{hbo} 
\]  

Where \( f \) is the oxygen extraction fraction, \( Q_{cara} \) (mL/min) is right coronary artery flow rate, \( S_{a1} \) is the arterial fractional oxyhemoglobin saturation, \( C_{hbo} \) (g/mL) is the concentration of hemoglobin, and 1.34 (mL/g) is the hemoglobin oxygen carrying capacity.

Setting the equilibrium between oxygen supply and demand and solving for CO we get:

\[
CO = \frac{O_2 \text{ sup} \times E_M}{0.0495 \bar{p}_{pa}} = \frac{27.1 fQ_{cara}S_{a1}C_{hbo}E_M}{\bar{p}_{pa}} 
\]

The calculation of mechanical efficiency from Eq. (2) is limited by the need to acquire instantaneous pulmonary artery flow rate, which is impossible with only PA catherization. Therefore we can use an alternate method for estimating mechanical efficiency wherein the stroke power, \( P_s \) is estimated as:

\[
P_s \sim CO^* p_{w,q} \sim HR^* SV^* p_{w,q} 
\]
where SV is the stroke volume. Substituting Eq. (9) into Eq. (2) and using the definition of mechanical efficiency in Eq. (4) we get:

\[
E_M = \frac{HR^* SV^* p_{rv,eq}}{HR(p_{rv,eq} - p_{rv,ed}) V_\infty + (HR^* SV^* p_{rv,eq})}
\]  

(10)

Dividing the top and bottom of Eq. (10) by SV and simplifying, we get:

\[
E_M = \frac{EF^* p_{rv,eq}}{p_{rv,eq}(1 + EF) - p_{rv,ed}}
\]  

(11)

where EF is the ejection fraction. Eq. (11) only requires knowing two pressures and EF, which can be achieved through PA catheterization with or without echocardiography.

2.2 Clinical Data

Through collaboration with the Pulmonary Hypertension Group at the VU University Medical Center in Amsterdam, Netherlands, we received RV hemodynamic data for 15 idiopathic pulmonary artery hypertension (IPAH) patients. Of the 15 patients (aged 26-71 years), 14 were female and 1 was male. Each patient was grouped according to the New York Heart Association Classification (NYHA). RV hemodynamic data was obtained through cardiac Magnetic Resonance Imaging, cardiac Positron Emission Tomography, and right heart catheterization. Pulmonary artery pressure, right ventricular pressure, and ECG data was recorded simultaneously (n=11) and asynchronously (n=4) during a cycling exercise test at a sampling rate of 1000Hz for a period of 5 minutes [4]. The details of this clinical study can be found in Wong et al [4].

2.3 Right Ventricular Ejection Time Interval Algorithms

In order to determine RV ejection pressure, a beat-by-beat RV pressure waveform derivative algorithm was used. This algorithm was based on the concept that the maximal positive rate of change in RV pressure (dP/dt max) corresponds to the opening of the pulmonic valve as the RV
rapidly contracts to generate blood flow and thus indicates the beginning of RV ejection (Fig. 1). Similarly, the maximal negative rate of change in RV pressure (dP/dt\text{min}) corresponds to the closing of the pulmonic valve and indicates the end of RV ejection (Fig. 1). The period between successive dP/dt\text{max} and dP/dt\text{min} is the RV ejection interval for a single heart beat (Fig. 1). For PAP and RVP waveforms that were recorded simultaneously (n=11), the ejection time interval obtained for each beat from the RVEP Algorithm was also the time period (T) from Eq. (2) over which PA pressure and flow were integrated to calculate stroke power.

![Figure 1. Beat-by-Beat RV Pressure Derivative Algorithm to Calculate RV Ejection Pressure](image)

This algorithm was implemented in MATLAB in the following way:

1. To eliminate noise from the RVP waveform, a 40 point moving average filter was applied. The moving average filter was the unweighted mean taken from 20 data points on either side of a central value to ensure that variations in the mean aligned with variations in the data.

2. RV dP/dt was calculated using arithmetic differentiation wherein dP/dt(i-1) = RVP(i) – RVP(i-1) and dt = 0.001s (1000Hz)
3. A local peak detection algorithm was used to determine the time indices at which 
\[ \frac{dP}{dt_{\text{max}}} \] (beginning of RV ejection) and \[ \frac{dP}{dt_{\text{min}}} \] (end of RV ejection) occurred. Maxima and minima that did not form a full heartbeat were excluded.

4. The RV ejection time interval was determined for each heartbeat

5. The RV ejection pressure (RVEP) values that corresponded to the ejection time interval were obtained and averaged to arrive at the mean RVEP for a single heartbeat

6. Finally, the mean RVEPs for all the beats were averaged to obtain the mean RVEP for each patient.

For asynchronous recordings (n=4), the RVEP algorithm was used only to calculate mean RVEP. An alternative method, described below, was used to determine RV ejection time interval (T) for each heartbeat. This was done to obtain the ejection time interval in terms of PA pressure time indices for stroke power integration calculation.

*Figure 2.* Beat-by-Beat PA Pressure Waveform Second Derivative Algorithm to Calculate Ejection Time Interval
The second derivative maxima of pulmonary artery pressure ($d^2P/dt^2_{\text{max}}$) indicate opening and closing of the pulmonary valve and can therefore be used to ascertain RV ejection time interval. A local peak detection algorithm was used to determine the time indices (corresponding to the PA pressure waveform) where $d^2P/dt^2$ maxima occurred (Fig. 2). RV ejection time interval for a single heartbeat was calculated as $t(d^2P/dt^2_{\text{max}}(i)) - t(d^2P/dt^2_{\text{max}}(i-1))$. To validate this method, both the RVP $dP/dt$ method and PAP $d^2P/dt^2$ method were performed on patients whose RV and PA pressure waveforms were recorded simultaneously ($n=11$). The stroke powers obtained from each method were then compared.

![Graph](image)

**Figure 3.** Comparison of stroke power calculated using the ejection time interval obtained from the pulmonary artery pressure waveform second derivative algorithm vs. the right ventricular pressure waveform first derivative algorithm.

RV stroke power determined using the PA pressure waveform second derivative algorithm was highly predictive ($R^2 = 0.985$) of that determined using the conventional RV pressure waveform first derivative algorithm with almost a one-to-one correspondence ($y = 0.959x + 1.997$) (Fig. 3). Therefore the PA pressure algorithm served as a valid alternative for determining ejection time.
interval (also the time period for stroke power integration) in patients whose RV and PA pressure recordings were asynchronous.

2.4 Model Accuracy Analysis

The relationship between myocardial energy expenditure (RV total power output) and RV oxygen consumption was assessed to determine the RV’s myocardial metabolic-mechanical relationship under high afterload. To validate the approximations made in the simplified model in Eq. (9), RV \( E_M \) determined by Eq. (2) (experimental RV \( E_M \)) and Eq. (9) (predicted RV \( E_M \)) was compared using linear regression. To determine the overall accuracy of the model itself, the calculated RV \( E_M \) was used to back-calculate a “predicted CO” using Eq. (7), which was then compared to the actual CO using linear regression.
CHAPTER 3
RESULTS
3.1 Right Ventricular Hemodynamics by NYHA Classification

<table>
<thead>
<tr>
<th></th>
<th>NYHA II (n=8)</th>
<th>NYHA III (n=4)</th>
<th>NYHA IV (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PA Pressure (mmHg)</td>
<td>47.4±11.7</td>
<td>58.8±13.3</td>
<td>65.3±22.9</td>
</tr>
<tr>
<td>(Measured)</td>
<td>mPAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RV Ejection Pressure</td>
<td>65.9±14</td>
<td>83.7±17.5</td>
<td>76.2±30.3</td>
</tr>
<tr>
<td>(mmHg) (Computed)</td>
<td>mRVEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td>5.6±0.9</td>
<td>4.2±1.1</td>
<td>3.5±1.4</td>
</tr>
<tr>
<td>(Measured)</td>
<td>CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Experimental Efficiency (%)</td>
<td>34.2±7</td>
<td>25.1±1.6</td>
<td>19.3±3.7</td>
</tr>
<tr>
<td>(Computed)</td>
<td>E_M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Mean Blood Flow (mL/min)</td>
<td>47.5±15.5</td>
<td>64.6±20.8</td>
<td>55.2±12.6</td>
</tr>
<tr>
<td>(Measured)</td>
<td>RV_MBF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Extraction Fraction</td>
<td>0.6±0.15</td>
<td>0.7±0.16</td>
<td>0.9±0.08</td>
</tr>
<tr>
<td>(Measured)</td>
<td>OEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Supply</td>
<td>4.5±1.9</td>
<td>7.5±1.7</td>
<td>8.1±2</td>
</tr>
<tr>
<td>(Measured)</td>
<td>O_2_Supply</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Summary of RV hemodynamic changes by NYHA classification (Mean ± Std Dev)

The IPAH patient population exhibited a diverse range of RV hemodynamics (Table 1). The model indicates that an increased afterload resulted in a decreased mechanical efficiency and CO (Table. 1). RV ejection pressure and mean blood flow increased from class II to class III but then remained relatively unchanged for the class III patients. The OEF increased with the severity of IPAH thereby suggesting some degree of compensation.
3.2 Model Accuracy

A positive linear correlation between the RV myocardial total power output and RV free wall oxygen consumption under high afterload ($R^2 = 0.68$) was observed (Fig. 4).

Figure 4. RV myocardial total power output (where $P_S$ was calculated using $mPAP$ and $CO$) vs. oxygen supply that was obtained using cardiac PET $^4$.

Based on the RV stroke power calculated using $mPAP$ and $CO$, the RV free wall myocardium expended approximately an average of 21 Joules of energy for every cm$^3$ of oxygen consumption (Fig. 4). For RV total power calculated using the flow simulation technique, the RV free wall myocardium expended approximately an average of 21.7 Joules of energy for every cm$^3$ of oxygen consumption ($R^2 = 0.63$) (Fig. 5). Several previous studies have quantified this relationship in normal isolated and in-vivo hearts $^{6\,7}$ and have found that the non-ischemic myocardium expends approximately 21J of energy per cm$^3$ of oxygen consumption $^{6\,7}$. These previous studies, however, focused on LV oxygen consumption in normal hearts. Our results, therefore, indicate that this relationship holds even for right ventricles experiencing a wide range of hemodynamics under a high afterload.
A negative linear correlation between the RV mechanical efficiency and RV free wall oxygen consumption ($R^2 = 0.66$) was observed (Fig. 6). Interestingly, patients that exhibited the highest oxygen consumption were predicted to have the lowest $E_M$ despite a high total power output (Fig. 4, 6) while the patients that exhibited the lowest oxygen consumption were predicted to have the highest $E_M$ despite having a low total power output (Fig. 4, 6).

**Figure 5.** RV myocardial total power output (where $P_S$ was calculated using the flow simulation algorithm and discrete PAP integration) vs. oxygen supply that was obtained using cardiac PET $^{[4]}$.

**Figure 6.** RV mechanical efficiency (where $P_S$ was calculated using mPAP and CO) vs. oxygen supply.
Fig. 7 Experimental RV efficiency (wherein $P_S$ was calculated using $mPAP$ and $CO$) vs. Predicted RV efficiency

Figure 7 shows predicted RV efficiency calculated using Eq. (11) and experimental RV efficiency calculated using Eq. (2) wherein mean PAP and CO were used to calculate RV stroke power. There is a strong agreement ($R^2 = 0.94$) between the two with almost a one-to-one correspondence (Fig. 7) thereby showing that the approximations made to simplify Eq. (2) to Eq. (11) were valid.

Figure 8. Actual $CO$ (L/min) vs. predicted $CO$ (L/min)
Figure 8. shows that there is a poor correlation ($R^2 = 0.22$) between the predicted CO calculated using experimental $E_M$ (wherein $P_S$ was calculated using mPAP and CO) in Eq. (8). Predicted CO calculated using experimental $E_M$ wherein $P_S$ was calculated using flow profile simulation and instantaneous PAP also showed a poor correlation with actual CO ($R^2 = 0.33$) (Fig. 9). The model was most accurate in predicting RV function in NYHA IV patients.

![Figure 9. Actual CO (L/min) vs. predicted CO (L/min)](image)
There is a clear trend that an increased afterload corresponds to a decreased $E_M$ and a correspondingly low $CO$ and vice versa (Table 1). The NYHA II patients had to work against a lower afterload than the other two groups and generated an average $RVEP$ that was 18 mmHg greater than the mPAP. They also exhibited the highest average $E_M$ and the lowest average $OEF$ and $RV MBF$ (Table 1), which could indicate that these patients were successfully compensating against the increased afterload.

Compared to NYHA II, the NYHA III patients exhibited an increased $RV MBF$ and $OEF$ perhaps to compensate for the increased oxygen demand against a higher afterload (Table 1). However, due to the increased afterload, more power was required to pressurize the blood for ejection (isovolumic power) thereby leaving less energy to generate an $RVEP$ that was substantially greater than the afterload (stroke power). This is apparent in the low $CO$ and $E_M$ of the NYHA III patients despite generating an average $RVEP$ that was 25 mmHg higher than the mPAP. In addition, patients that exhibited the highest oxygen consumption were predicted to have the lowest $E_M$ despite a high total power output. This re-confirms our finding that under a high afterload majority of RV myocardial energy is spent on performing pressure work rather than volume work. 3 out of the 4 NYHA III patients exhibited a close to normal $CO$ possibly due to their ability to compensate with a higher $OEF$ and/or $RV MBF$ that allowed them to generate a $RVEP$ that was sufficiently higher than the afterload (Table 1). The fourth NYHA III patient exhibited an extremely low $CO$ of 2.6L/min despite having a similar $RVEP$ (74 mmHg), $E_M$ (27%), $RV MBF$ (48mL/min), and $OEF$ (0.8) compared to the other class III patients (Fig. 4, Table 1). In this case, the patient’s $CO$ was much lower than what the $E_M$ would predict.
The NYHA IV patients exhibited the highest $OEF$ and a relatively high $RV MBF$ compared to the other groups. Additionally, two of the three NYHA IV patients were pumping against an afterload that was not significantly higher than that experienced by the NYHA II and III groups. Despite this, NYHA IV patients exhibited the lowest $E_M$ and generated an $RVEP$ that was on average only 10 mmHg higher than the afterload (Table. 1). One of the NYHA IV patients exhibited a low $E_M$ of 16% and a corresponding $CO$ of 2.3L/min despite an extremely high $RVEP$ (108 mmHg) and a relatively high $OEF$ (0.77) and $RV MBF$ (61mL/min). Thus the model is able to distinguish between patients with similar afterloads and $RVEPs$ very well by taking into account differences in myocardial oxygen consumption.

There was a poor agreement between predicted $CO$ and actual $CO$ ($R^2 = 0.33$) (Fig. 5). This is surprising as the model is able to account for outliers such as the NYHA IV patient with a predicted $CO$ of 5.6L/min (Fig. 5) despite a predicted $E_M$ of 23%. One possible explanation could be that since Elbeery’s LV model that we adapted for the RV is based on canine data, it may not accurately model RV behavior in humans. Additionally, since predicted $E_M$ is highly dependent on $EF$ ($SV/EDV$), which also directly corresponds to $CO$, a possible source of error could be in RV end-diastolic volume measurements. Because RV $EDV$ measurements are dependent on the complex RV geometry, they are often inaccurate; especially in IPAH as the RV could be in an over-dilated or hypertrophied state. Furthermore since $SV$ is a small fraction of $EDV$ in IPAH patients, even moderate inaccuracies in $EDV$ measurements could result in large errors in $EF$. Taking a closer look at the patients whose predicted $CO$s were far lower than the actual $CO$s (4.8, 4.7, 6.45, 6.95 L/min), we find that their respective $EF$s were also relatively low (31, 52, 50, 65 %). Another reason for inaccurate $CO$ predictions could be due to the fact that the stroke power for NYHA II and III patients was very low in comparison to isovolumic power and
seemed to have a small role in oxygen consumption. In turn, $CO$ was a very small fraction of that stroke power and in modeling terms, it was an extremely small signal to a lot of isovolumic noise. Therefore a possible improvement to the model would be to use isovolumic power instead of stroke power to arrive at an alternative predictive index of RV strain.

Overall the model effectively related RV mechanical function to myocardial oxygen consumption and could be a useful tool for analyzing the extent of RV loading and how well a patient is able to accommodate by increasing myocardial oxygen supply. Although the implementation of the model requires the patient to undergo invasive and expensive clinical procedures such as cardiac PET, MRI, and right heart catherization, it is able to provide an intuitive, quantitative, and clinically relevant means for analyzing the patient’s ability to compensate against a high afterload in both mechanical and metabolic terms. However, as a predictive tool, the model is limited by the need to know the patient’s right coronary reserve to determine if $CO$ would decrease or remain the same if there was a further increase in afterload.
CHAPTER 5
CONCLUSION

This study shows that under a high afterload, RV mechanical power output is constrained by its oxygen supply. Evaluating the model in IPAH patients showed that an elevated afterload corresponded to a decrease in RV mechanical efficiency ($E_M$) and a corresponding decrease in CO. NYHA II patients that experienced a relatively low afterload compared to the other two groups exhibited the highest $E_M$ and lowest average myocardial oxygen supply (RV MBF and OEF). On the other hand, NYHA III and IV patients that experienced a high afterload exhibited low $E_M$ despite a high oxygen supply. The model suggests that a decrease in $E_M$ despite an increase in oxygen supply is caused by the use of the majority of myocardial energy to perform pressure work (isovolumic contraction) instead of volume work (ejection). Overall, the model was able to accurately distinguish patient hemodynamics despite similarities in mPAP and RVEP except for a few outliers possibly due to measurement errors in RV EDV caused by changes in RV geometry common to IPAH patients such as hypertrophy or over-dilation.

This biomechanical metabolic model effectively relates RV mechanical performance to myocardial oxygen metabolism and could be a useful clinical tool for analyzing the extent of increased RV loading and how well a patient has accommodated by increasing oxygen supply. A longitudinal clinical study with a larger number of patients would be necessary to further evaluate the model under high afterloads and develop a more accurate predictive index of RV failure.
APPENDIX

MATLAB Code to Calculate Stroke Power

%% Calculate Stroke Power

%% Load Time, RVP, Stroke Volume, and Cardiac Output Data

prompt1 = 'Enter Patient Excel Filename Ex. name.xlsx';
prompt2 = 'Enter Excel Range of Time Values Ex. A3:A500';
prompt3 = 'Enter Excel Range of Corresponding RVP Values Ex. B3:B500';
prompt4 = 'Enter Excel Range of Corresponding PAP Values';
prompt5 = 'Enter Stroke Volume (mL)';
prompt6 = 'Enter Cardiac Output (in mL/s)';

name1 = input(prompt1);
t_range = input(prompt2);
RVP_range = input(prompt3);
PAP_range = input(prompt4);

Stroke_Volume = input(prompt5);
CO = input(prompt6);

if length(t_range) ~= length(RVP_range)
    error('Input Time and RVP ranges must be the same');
end
[t1,RVP_mm,PAP] = loadRVP1(name1,t_range,RVP_range,PAP_range);

hold on
plot(t1,RVP_mm,'red')
legend('Unsmoothed RVP')

%% Smooth RVP Data, Calculate RVP dP/dt, Smooth dP/dt, Calculate d(dP/dt)/dt

prompt7 = 'Enter span for RVP smoothing';
prompt8 = 'Enter dt value';
n1 = input(prompt7);
dt = input(prompt8);
RVP = smooth(RVP_mm,n1);
[t_dt, dP_dt] = derivative(t1,RVP_mm,dt);
prompt9 = 'Enter span for dP/dt smoothing';
n = input(prompt9);
[smoothed_dP] = smoothRVP(dP_dt,n,t_dt);

%% Find local dP/dt max and min values and corresponding time values that indicate the beginning and end of RV ejection respectively
[min_pks_all, min_locs_all] = findpeaks(-smoothed_dP, 'minpeakdistance', 370);
[max_pks_all, max_locs_all] = findpeaks(smoothed_dP, 'minpeakdistance', 370);

min_time = t_dt(min_locs_all);
max_time = t_dt(max_locs_all);

clf
hold on
plot(t_dt, smoothed_dP, 'red')
plot(min_time, -min_pks_all, 'g*')
plot(max_time, max_pks_all, 'y*')

disp('Number of total max dP/dt peaks detected: ')
disp(length(max_pks_all))
disp('Number of total min dP/dt peaks detected: ')
disp(length(min_pks_all))

%%% Choose how many heart beats to include in RV Ejection Pressure Calculation

prompt10 = 'Enter 1st max peak location (integer only)';
prompt11 = 'Enter last max peak location (integer only)';
prompt12 = 'Enter 1st min peak location (integer only)';
prompt13 = 'Enter last min peak location (integer only)';

max_pk_start = input(prompt10);
max_pk_end = input(prompt11);
min_pk_start = input(prompt12);
min_pk_end = input(prompt13);

min_pks = min_pks_all(min_pk_start:min_pk_end);
max_pks = max_pks_all(max_pk_start:max_pk_end);

min_time = t_dt(min_locs_all(min_pk_start:min_pk_end))';
max_time = t_dt(max_locs_all(max_pk_start:max_pk_end))';

min_locs = min_locs_all(min_pk_start:min_pk_end);
max_locs = max_locs_all(max_pk_start:max_pk_end);

max_info = [max_time, max_pks];
min_info = [min_time, -min_pks];

%%% Find RVP values that correspond to dP/dt max and min values aka start and end of ejection and calculate average ejection pressure

[mean_systolic_RVP, dP_max_locations, dP_min_locations, RVP_systole_start, RVP_systole_end] = findtimeindices(max_info, min_info, t_dt, RVP);
disp('Mean Systolic RVP: ')
disp(mean_systolic_RVP)
cf
hold on
plot(d1,RVP,'blue')
plot(dP_max_locations,RVP_systole_start,'c*')
plot(dP_min_locations,RVP_systole_end,'r*')
hold off
plot(min_RVP_time,-min_pks_RV,'g*')
legend('RVP','Systole Start','Systole End')

%% Flow Profile Simulation

sti = num2cell(zeros(1,5)); %Systolic Time Interval
tss = num2cell(dP_max_locations(1:1:5)/10); %Time at which systole starts
tes = num2cell(dP_min_locations(1:1:5)/10); %Time at which systole ends
ted = num2cell(dP_max_locations(2:1:6)/10); %Time at which diastole ends

% Loop below saves flow and time data for each in cell arrays but all % calculations are done in numeric arrays for simplicity

for i = 1:5
    sti{i} = tes{i} - tss{i};
t_x_1{i} = num2cell(tss{i}:0.0001:tes{i}); %Time interval over which systole occurs
    t_x_2{i} = num2cell(tes{i}:0.0001:tes{i}+0.002); %Time interval over which regurgitation occurs
    t_x_3{i} = num2cell(tes{i}+0.002:0.0001:ted{i}); %Time interval over which diastole occurs
end

Qx_1 = zeros(size(t_x_1));
Qx_2 = zeros(size(t_x_2));
Qx_3 = zeros(size(t_x_3));
Ax = 1; %Start with a systolic sine wave amplitude of 1
tss_x = cell2mat(tss(i));
sti_x = cell2mat(sti(i));
t_x1 = cell2mat(t_x_1{i});
t_x2 = cell2mat(t_x_2{i});
t_x3 = cell2mat(t_x_3{i});

for j = 1:length(t_x1)
    Qx_1(j) = Ax*Stroke_Volume*(exp((-3*(t_x1(j)-tss_x)))*sin((pi*(t_x1(j)-tss_x))/sti_x)); %Systolic Flow
end
Qx_1(end) = 0;
for k = 1:length(t_x2)
    Qx_2(k) = Qx_1(length(Qx_1))*(1-((t_x2(k)-sti_x-0.02)/0.02)); %Regurgitant Flow
end
for l = 1:length(t_x3)
Qx_3(l) = 0; %Diastolic Flow
end
Qx = [Qx_1, Qx_2, Qx_3]; %Flow for a single Heart Beat (Systole+Regurgitation+Diastole)
eval(['Flow num2str(i) ' = Qx;']);
Qxx{i} = num2cell(Qx); %Stores total invented flow for each heart beat in a cell array
end

Inv_Flow = {Flow1, Flow2, Flow3, Flow4, Flow5}; %Invented Flow without amplitude adjustment

% Adjust Invented Flow Amplitude such that average invented flow across 5 heart beats matches cardiac output
Amp = 1;
if mean(cell2mat(Inv_Flow))<CO
    Amp = (Amp/mean(cell2mat(Inv_Flow)))*CO;
    for i = 1:5
        Flowx = Inv_Flow{i}*Amp;
        eval(['Flow' num2str(i) ' = Flowx;']);
        t_Q = [cell2mat(t_x_1{i}), cell2mat(t_x_2{i}), cell2mat(t_x_3{i})];
        eval(['t_Q' num2str(i) ' = t_Q;']);
    end
end

Inv_Flow = {Flow1, Flow2, Flow3, Flow4, Flow5};

clf
hold on
plot(t_Q1, Flow1)
plot(t_Q2, Flow2)
plot(t_Q3, Flow3)
plot(t_Q4, Flow4)
plot(t_Q5, Flow5)
legend('Invented Pulmonary Artery Flow (mL/s)')

%% Calculate Mean Flow, Peak Flow and Ejection Time Interval
for i = 1:5
    Q = Inv_Flow{i};
    Peak_Flow(i) = max(Q);
end

disp('Mean Flow over 5 Heart Beats:')
disp(mean(cell2mat(Inv_Flow)))
disp('Peak Flow for each Heart Beat:')
disp(Peak_Flow)
disp('Ejection Time Interval for each Heart Beat: ')
disp(sti)

%% Integrate to Calculate Stroke Power

PAP_int = {5};

for i = 1:5
    start_PAFlow = 1;
    PAFlow_ejectime = cell2mat(t_x_1{i});
    end_PAFlow(i) = length(PAFlow_ejectime);

    PAP_int{i} = num2cell(PAP(max_locs(i):min_locs(i)));
    PAP_period{i} = num2cell(t1(max_locs(i):min_locs(i)));

    Q = Inv_Flow{i};
    PAFlow_int{i} = num2cell(Q(start_PAFlow:end_PAFlow(i)));
    int_x = cell2mat(PAP_int{i}').*cell2mat(PAFlow_int{i});
    int{i} = num2cell([int_x]);

    strokework{i} = trapz(cell2mat(t_x_1{i})*10,cell2mat(int{i}));

    time_int(i) = (ted{i}-tss{i})*10;
    strokepower(i) = strokework{i}/time_int(i);
end

Avg_strokepower = mean(strokepower)

Associated Functions:

function [t_dt, dP_dt] = derivative(t1,RVP,dt)

    t_differential_start = t1(1)+(dt/2);
    t_differential_end = t1(length(t1))-(dt/2);

    t_interp_start = t1(1);
    t_interp_end = t1(length(t1));

    %% Calculate the derivative of RVP; dP/dt and interpolate

    for i = 2:length(RVP)
        dP(i-1) = RVP(i)-RVP(i-1);
    end

    %% Interpolate dP/dt values such that dP and dt vectors match with
    %% original RVP and time vectors

    t_differential = [t_differential_start:dt:t_differential_end];
    t_dt = [t_interp_start:dt:t_interp_end];
dP_dt = interp1(t_differential,dP,t_dt,'spline');

hold on
plot(t_dt,dP_dt,'red')
legend('dP/dt')
end

function
[mean_systolic_RVP,dP_max_locations,dP_min_locations,RVP_systole_start,RVP_systole_end] = findtimeindices(max_info,min_info,t_dt,RVP)

%Utilize Time Indices of dP/dt max and min to find corresponding RVP values that will define the beginning and end of systole respectively

dP_max_locations = max_info(:,1); %Time values/locations of dP/dt max values

dP_min_locations = min_info(:,1); %Time values/locations of dP/dt min values

%Find the time indices of t_dt that correspond to the time values of dP/dt max values
b = []; for i = 1:length(dP_max_locations) a = dP_max_locations(i); b = [b find(t_dt==a)]; end

%Find the time indices of t_dt that correspond to the time values of dP/dt min values
d = []; for i = 1:length(dP_min_locations) c = dP_min_locations(i); d = [d find(t_dt==c)]; end

%Account for peakdetect function output having different number of max and min values
if length(b) > length(d) for i = 1:length(d) new_b(i) = b(i); end
for i = 1:length(d)
    systolic_RVP(i) = mean(RVP(new_b(i):d(i)));
end

mean_systolic_RVP = mean(systolic_RVP);
RVP_systole_start = RVP(new_b);
RVP_systole_end = RVP(d);
dP_max_locations = dP_max_locations(1:length(new_b));
end

if length(d) > length(b)
    for i = 1:length(b)
        new_d(i) = d(i);
    end

    for i = 1:length(b)
        systolic_RVP(i) = mean(RVP(b(i):new_d(i)));
    end

    mean_systolic_RVP = mean(systolic_RVP);
    RVP_systole_start = RVP(b);
    RVP_systole_end = RVP(new_d);
dP_min_locations = dP_min_locations(1:length(new_d));
end

if length(b) == length(d)
    for i = 1:length(b)
        systolic_RVP(i) = mean(RVP(b(i):d(i)));
    end

    mean_systolic_RVP = mean(systolic_RVP);
    RVP_systole_start = RVP(b);
    RVP_systole_end = RVP(d);
end
end
REFERENCES
