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Development of an adaptive pulmonary simulator for *in vitro* analysis of patient populations and patient-specific data

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ABSTRACT

Background and objective: Patient-specific modeling (PSM) is gaining more attention from researchers due to its ability to potentially improve diagnostic capabilities, guide the design of intervention procedures, and optimize clinical management by predicting the outcome of a particular treatment and/or surgical intervention. Due to the hemodynamic diversity of specific patients, an adaptive pulmonary simulator (PS) would be essential for analyzing the possible impact of external factors on the safety, performance, and reliability of a cardiac assist device within a mock circulatory system (MCS). In order to accurately and precisely replicate the conditions within the pulmonary system, a PS should not only account for the ability of the pulmonary system to supply blood flow at specific pressures, but similarly consider systemic outflow dynamics. This would provide an accurate pressure and flow rate return supply back into the left ventricular section of the MCS (i.e. the initial conditions of the left heart).
Methods: Employing an embedded Windkessel model, a control system model was developed utilizing MathWorks' Simulink® Simscape™. Following a verification and validation (V&V) analysis approach, a PI-controlled closed-loop hydraulic system was developed using Simscape™. This physical system modeling tool was used to (1) develop and control the *in silico* system during verification studies and (2) simulate pulmonary performance for validation of this control architecture.
Results: The pulmonary Windkessel model developed is capable of generating the left atrial pressure (LAP) waveform from given pulmonary factors, aortic conditions, and systemic variables. Verification of the adaptive PS's performance and validation of this control architecture support this modeling methodology as an effective means of reproducing pulmonary pressure waveforms and systemic outflow conditions, unique to a particular patient. Adult and geriatric with and without Heart Failure and a Normal Ejection Fraction (HFNEF) are presented.
Conclusions: The adaptability of this modelling approach allows for the simulation of pulmonary conditions without the limitations of a dedicated hardware platform for use in *in vitro* investigations.

1. Introduction

Patient-specific modeling (PSM) is the development of a personalized computational model of a patient's pathophysiology that is unique to that individual's patient-specific data. According to the 2009 survey of recent advancements in the field of PSM by Neal and Kerckhoffs [1], this form of modeling is gaining more consideration from researchers due to its potential to improve diagnostic capabilities, optimize clinical treatment, and guide the design of intervention procedures by predicting the outcome of a particular therapy and/or surgical interventions. Presently, most medical diagnostic practices lead to rough estimations of a particular treatment plan's effectiveness, to which these randomized clinical trial results are the foundation for individual patient treatment plans [2]. Unfortunately, these results might not directly apply to the needs of every individual patient since these results are based on the limited averages of a randomized study [3]. As an alternative, PSM can be utilized as a theranostic tool to personalize an individual's treatment strategy and optimize their remediation therapy to fit their needs more appropriately. This can be achieved through

Abbreviations: (AoP) [mmHg], Aortic Pressure; (HFNEF), Heart Failure with Normal Ejection Fraction; (LAP) [mmHg], Left Atrial Pressure; (LVAD), Left Ventricular Assist Device; (LVIF), equivalent to Mitral Valve Flow Rate [$cm^3\ s^{-1}$], Left Ventricular Inflow; (LVOF), equivalent to Aortic Valve Flow Rate [$cm^3\ s^{-1}$], Left Ventricular Outflow; (LVP) [mmHg], Left Ventricular Pressure; (MCS), Mock Circulatory System; (PSM), Patient-specific modeling; (PI) Controller, Proportional-Integral; (PS), Pulmonary Simulator; (RCL), Resistor-Capacitor-Inductor; (RMSE), Root-Mean-Square Error; (VAD), Ventricular Assist Device; (V&V), Verification and Validation.

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PSM by obtaining immeasurable information, such as data regarding the interrelationship between the safety and reliability of a cardiac assist device and an individual's unique pathophysiological conditions, which cannot be quantitatively measured *in vivo*. This strategy may serve as a better predictor of the probability that a particular individual's treatment plan will be effective.

According to the American Heart Association's Heart Disease and Stroke Statistics – 2017 Update [4], approximately 6.5 million people in the United States alone suffer from varying degrees of heart failure, while approximately half of the people who develop heart failure will die within 5 years of diagnosis [5]. One alternative is the support from a cardiac assist system, such as a left ventricular assist device (LVAD), to directly assist with the blood flow demands of systemic, and subsequently pulmonary circulation [6]. A LVAD's primary function is to offer circulatory support to the heart by effectively pumping blood directly to the aorta, from the left ventricle, bypassing a possibly impaired aortic valve.

While a circulatory hemodynamic model is not a substitute for *in vivo* investigations, an LVAD's design can be effectively refined beforehand by determining its influence on cardiac hemodynamics. This is accomplished through the use of a mock circulatory system (MCS), which simulates the human circulatory system in a benchtop hydraulic circuit that accurately and precisely replicates time-dependent cardiovascular hemodynamic conditions [7]. Due to the complexity of the cardiovascular system and the dynamics related to cardiac functionality, a MCS is a necessary *in vitro* tool used to effectively test cardiac assist technologies [8]. Primarily, published research efforts include methods of MCS development [7,9–13] and the results of *in vitro* investigations [14–16].

In 2009 (updated from original document published in 1998), a collaboration between the FDA, The American Society for Artificial Internal Organs (ASAIO), the Society of Thoracic Surgeons (STS), and the National Heart, Lung, and Blood Institute published an article in ASAIO Journal entitled, "Long-Term Mechanical Circulatory Support System Reliability Recommendation by the National Clinical Trial Initiative Subcommittee" [17,8]. In these articles, suggested conditions that must be accounted for in order to evaluate a blood pump in a hydraulic circulatory model of human hemodynamic, are discussed. Additional guidance documents used for assessment reaffirm this articles recommendation: ISO 5198, ISO 14708, and ISO 14791. In their requirements, appropriate conditions to properly assess different patient populations are addressed. As a MCS inlet condition generator and adaptable preload system, an adaptive pulmonary simulator (PS) would satisfy those conditions for any patient populations (i.e. pediatric, adult, and geriatric). Additionally, this approach would provide the ability to generate a range of left atrial pressure (LAP) related physiological and pathophysiological conditions, necessary for patient-specific analysis.

This manuscript is organized as follows. Section 2 outlines the theory governing Windkessel modeling, its background in simulating cardiovascular hemodynamics, and what a pulmonary simulator should contain for subsequent *in vitro* testing. In Section 3, we present the proposed methodology for simulating pulmonary functionality. Section 4 reveals the experimental results and Section 5 concludes with a discussion.

2. Theoretical background

2.1. Cardiovascular system modeling

Computational modeling of the human cardiovascular system has been established to be an effective research tool [18]. Preliminary investigations into the usefulness of cardiovascular system modeling was established by John McLeod in 1966 [19,20]. PHYSBE, the physiological simulator, was developed to investigate the bloodstream as a transport mechanism. It was capable of demonstrating a variety of normal and abnormal physiological functions, such as oxygen and carbon dioxide transport; as well as replicate normal and pathological conditions, such as weakened left or right ventricular action. Subsequently, many cardiovascular computational models have been developed as a tool dedicated to circulatory system understanding [19–26] or educational training [27–30]. With the advent of novel approaches, tools, and software, the potential applications as a hemodynamic response predictor for patient-specific investigations is expanding [18,31–34].

2.2. Windkessel modeling

A Windkessel model is a computational approach using electrical circuit elements that exploits a phenomenon known as the Windkessel effect. This effect accounts for the characteristics of the arterial blood pressure waveform in terms of the interaction between stroke volume and the compliance of the aorta and large elastic arteries, known as the Windkessel vessels [35]. Utilizing this technique, elements of a resistor-capacitor-inductor (RCL) circuit can be related to its analogous anatomical equivalent within the circulatory system. Peripheral resistance (viscous properties of blood flow) is analogous to a resistor, arterial compliance (elastic properties of the vessel walls) to a capacitor, and an inductor to the inertia of blood. Key analogous quantities that relate electrical components to their corresponding hydraulic counterpart are known to be voltage and current (electrical) with pressure and flow rate (hydraulic), respectively. In this manner, the entire cardiovascular system can be simulated using this lumped parameter modeling technique.

Efforts have been made to evaluate the usefulness of modeling the cardiovascular system utilizing the Windkessel modeling technique to include the research conducted in 2013 by de Canete et al. [21]. In their study, the complete cardiovascular system was modeled as a closed loop electrical circuit using the MathWorks' Simulink® Simscape™ tools. By simply modifying either the structure of the electrical circuit or key parameters of the analogous cardiovascular electrical element, their object-oriented approach can simulate a range of physiological and pathophysiological conditions to include: physical exercise, heart failure, hypertension, changes in peripheral resistance, aortic insufficiency, hemorrhage, hypervolemia, renal diseases, valvular pathologies, etc.

Other research efforts regarding cardiovascular physiology simulators using equivalent electronic circuits include the research conducted by Rupnik et al. [29,30]. Their complete cardiovascular system allows for the simulation of various normal as well as pathological states, such as the effects of heart rate changes, heart failure, negative intrathoracic pressure, exercise, hemorrhage, and hypertension. Additional simulators using equivalent electrical circuits include the research completed by Sever et al. [36], regarding the simulation of acute left ventricle failure and exercise in patients with aortic stenosis and the research conducted by Avanzolini et al. [37] regarding the simulation of the time-varying mechanical properties of the left ventricle.

Additionally, research has evaluated the efficacy of utilizing a Windkessel cardiovascular system model to guide *in vitro* investigations. In 1985, McInnis et al. [38] demonstrated that a left ventricular bypass assist device consisting of air driven diaphragm is capable of being driven and controlled utilizing an electrical circuit analog model of the circulatory system. In 2011, Timms et al. [12] demonstrated that a five element Windkessel-based computer simulation model can be used to assist the design and selections of appropriate cardiovascular parameters for each segment of a MCS for the *in vitro* testing of cardiovascular assist devices. Then in 2011, Ferrari et al. [39] developed a modular computational Windkessel model able to interact with a ventricular assist device (VAD) for research and educational applications. Their investigation was