Mathematical modeling and simulation allows for an in-depth examination of the cardiovascular system and provides the opportunity to develop deeper understanding. This review summarizes recent efforts at modeling the cardiovascular system and how these models have been useful in providing greater comprehension of the pathophysiology of heart failure, explaining the hemodynamic impact of various heart failure devices, predicting the hemodynamic effects and clinical outcomes of certain heart failure clinical trials, and perhaps aiding in patient selection for new therapies. The potential future use of these models in clinical research and clinical practice are also discussed. (J Cardiac Fail 2016;22:303–311)

Key Words: Cardiovascular modeling, simulation, hemodynamics.

The heart and vasculature have been the topic of research for more than a century, with countless efforts made to mathematically model their properties. More than 50 years ago, researchers also started focusing on coupling vascular and cardiac models to understand the determinants of key clinically important hemodynamic parameters. These models have undergone tremendous evolution over the years. Some of the more recent embodiments start with mathematical representations of myocyte function based on actin-myosin interactions, ion channel function, ion metabolism (sodium, calcium, potassium, etc.), and models of signaling pathways. Based on those building blocks, a heart with realistic chamber geometries, myocyte fiber orientations, and valves is constructed. That model heart then interacts with complex models of the pulmonary and systemic vascular systems. Some of these models even include short- and long-term adaptations based on simulated autonomic nervous systems and molecular responses of the heart, vasculature, and kidneys to acute and chronic mechanical and neurohormonal stimuli. Such models require significant computing power and computing time and are not readily available or convenient for real time use.

In contrast, simpler models employing high-level phenomenological descriptions of heart chamber properties based on pressure-volume relationships and 0-order representations of the vascular systems have also been developed. Although these simpler models provide less detailed predictions of pressure and flow waveforms, they have shown great flexibility in simulating the hemodynamics of a very wide range of heart failure–related disease states and therapies while retaining the ability to be run in real time, even on desktop, laptop, and mobile devices.

This review summarizes the current status of these recent efforts at simple cardiovascular modeling and how they have been useful in providing insights into pathophysiology of heart failure, explaining hemodynamic impact of different heart failure devices and surgeries, predicting the hemodynamic effects and outcomes of certain clinical trials, and guiding selected aspects of patient selection for new therapies. The potential future uses of these simpler models in clinical research and clinical practice are discussed.

Overview of Simple Cardiovascular Models

Modern simulations of the cardiovascular system have their origin in the work of Guyton, who described the systemic and pulmonary vascular systems by series of resistance and compliance elements. Suga and Sagawa introduced the time-varying elastance model to describe the time-dependent, load-
independent dynamics of atrial and ventricular contraction. Sunagawa and colleagues coupled the time-varying elastance model of the heart to the Guytonian model of the vasculature systems, which led to the ability to describe the time-dependence of pressure, flow, and volume waveforms in the ventricles, atria, arteries, and veins. Collectively, these efforts provided the foundation for developing comprehensive, integrated models of the complete cardiovascular system in health and disease, including the introduction of certain types of devices (e.g., blood pumps), valve lesions, and shunts. The details of the model have been provided previously (including the differential equations underlying the model) and are summarized more fully in the online supplemental material. The differential equations describing such models can be solved with simple mathematical techniques yielding a multitude of outputs, including the pressure-volume loops from each of the 4 chambers (Fig. 1); time-dependent tracings of pressures, flows, and volumes; and all of the possible hemodynamic parameters derived from these signals. Note in Fig. 1 (in which all loops and time-dependent tracing are derived directly from the simulation) that the pressure-volume loops of the normal right ventricle and of each atrium are significantly different than those of the more familiar normal left ventricle, and that these simulated loops have all key characteristics of directly measured loops reported in the literature.

Potential Applications of Cardiovascular Modeling

There are at least 4 interrelated areas where cardiovascular hemodynamic modeling is of potential clinical utility: (1) clarifying fundamental hemodynamic principles related to pathophysiology of disease and therapeutic approaches; (2) predicting the hemodynamic effects and outcomes of certain clinical trials; (3) assisting in device development; and (4) guiding selection of cardiovascular therapeutics in individual patients. A summary of key applications and, when available, references that provide data to support conclusions derived from the model are summarized in
Table 1. Examples of Where the “Simple” Modeling Approach has Been Used in Cardiovascular and Heart Failure Research, Along With Experimental Validation Studies When Available

<table>
<thead>
<tr>
<th>Clinical Observation</th>
<th>Reference</th>
<th>Supporting Data</th>
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<tr>
<td>Explained basic clinical observations:</td>
<td>6</td>
<td>12,13</td>
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<tr>
<td>- Revealed the critical role of reflex-mediated venoconstriction in the generation of pulmonary congestion in the setting of LV dysfunction.</td>
<td>14</td>
<td>12,15,16-17</td>
</tr>
<tr>
<td>- Clarification of the role of time constant of relaxation (τ) on LV end-diastolic pressure.</td>
<td>18</td>
<td>NA</td>
</tr>
<tr>
<td>- Clarification of the hemodynamic consequences of ventricular interdependence.</td>
<td>19</td>
<td>NA</td>
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<tr>
<td>- Explains the effects of different types of mechanical circulatory support devices on ventricular-pressure-volume loops and energetics.</td>
<td>20</td>
<td>21-23</td>
</tr>
<tr>
<td>- Explains why the left ventricle can become overloaded when treating patients with ADHF with ECMO.</td>
<td>20</td>
<td>24,25</td>
</tr>
<tr>
<td>Predicting hemodynamic impact of device-based therapies and help guide patient selection:</td>
<td></td>
<td></td>
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<tr>
<td>- Prospectively predicted impact of a new partial support device/strategy in patients with chronic heart failure.</td>
<td>26</td>
<td>26,27</td>
</tr>
<tr>
<td>- Prospectively predicted impact of an interatrial shunt on resting pulmonary capillary wedge pressure in patients with HFpEF.</td>
<td>26</td>
<td>29,30</td>
</tr>
<tr>
<td>Prospective predicted results of clinical trials based on explanation of physiological principles:</td>
<td></td>
<td></td>
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<tr>
<td>- Demonstrated that Batista operation would be detrimental to patients with idiopathic cardiomyopathy.</td>
<td>31</td>
<td>32-34</td>
</tr>
<tr>
<td>- Demonstrated that the surgical ventricular reconstruction (i.e., the Dor procedure) would have a neutral effect on LV function and mortality.</td>
<td>35,36</td>
<td>37-39</td>
</tr>
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</table>

ADHF, acute decompensated heart failure; ECMO, extracorporeal membrane oxygenation; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular.

Table 1: these are detailed further in the following sections. It should be noted that efforts to date have focused on developing and retrospectively validating the modeling approach, and that prospective validation of these applications is ongoing.

Elucidation of Clinically Important Hemodynamic Principles

Key examples in which this modeling approach has helped elucidate hemodynamic principles, and mechanisms of disease include clarification of: (1) the role of reflex-mediated venoconstriction in the pathogenesis of acute pulmonary congestion in the setting of acute left ventricular (LV) dysfunction; (2) why pulmonary edema can occur with use of pulmonary vasodilator therapy in patients with pulmonary hypertension; (3) the impact of changes in the time constant of relaxation at different heart rates; and (4) the physiological significance of interventricular interactions in health and disease. The first 2 examples have recently received independent validation from clinical data. Direct clinical validation of the role of interventricular interactions and of prolongation of the time constant of relaxation is difficult (or impossible) because of the inability to solely vary the parameter in question. In such cases, modeling provides insights that would otherwise be unavailable.

Cardiovascular simulation has also been employed to characterize and explain otherwise unrecognized differences and consequences in hemodynamic effects among commonly used forms of acute, percutaneously deployable mechanical circulatory support (MCS) devices. These devices include intraaortic balloon pumps, transaortic valvular left ventricle-to-aorta pumping, left atrial-to-aortic pumping and right atrial-to-aortic pumping (the typical configuration for extracorporeal membrane oxygenation, ECMO). Although all these forms of MCS increase total blood flow to the body and increase blood pressure, they differ with regard to the amount and nature of LV unloading, their impact on pulmonary capillary wedge pressure, and, consequently, on the degree to which myocardial oxygen demand is modified, as discussed previously. Experiments in animals and humans have confirmed the impact of some of these devices on LV pressure-volume loops; two examples are shown in Fig. 2. In the top panel, predicted changes in the pressure-volume loops from baseline (solid line) in response to mechanical circulatory support pumping blood from the left ventricle to the aorta (dotted line) or from the left atrium to the aorta (dashed line) are shown. Left ventricle-to-aorta pumping results in a triangular-shaped pressure-volume loop with reductions in both end-diastolic and end-systolic volumes. Left atrium-to-aorta pumping results in a narrowed rectangular-shaped loop with reduction in end-diastolic volume but unchanged or increased end-systolic volume. Experimental recordings confirming these predictions are shown in Fig. 2B and C. The hemodynamic, energetic, and potential clinical implications of these differences have been detailed previously.

Finally, efforts directly guided by the model are under way to elucidate key aspects of the hemodynamics of ECMO, specifically to understand in which patients ECMO will cause pulmonary edema without the use of an LV unloading strategy.

Device Development and Early Clinical Evaluation

Cardiovascular modeling has the potential to contribute to design specifications of certain types of devices and, by predicting hemodynamic effects of a new device under clinically relevant conditions, can contribute to establishment of inclusion and exclusion criteria for early clinical trials of new devices especially when no appropriate animal models exist to test principles of operation. Two recent examples illustrate these points.

First was the use of simulation during the early development of the Synergy partial LV assist device intended for patients with end-stage heart failure, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory
Support) profile $\geq 4$. This device pumps blood from the left atrium to the right subclavian artery at a flow rate between 2 and 3 L/min. Before introduction into the clinic, preclinical studies were done to clarify its hemodynamic effects and confirmed that the model successfully predicted those effects in animals. For the average patient enrolled in the study, the simulation predicted an ~10 mmHg decrease in pulmonary capillary wedge pressure (PCWP) and an increase in total blood flow (device plus heart) of between one-third and one-half (not equal to) the rate of flow of the device itself (Fig. 3A and B). It was clarified that the reason why total flow does not simply increase by the same amount as the pump flow is because the decreased preload and increased afterload on the native heart resulting from left atrial-to-arterial pumping reduces native LV output. These simulation predictions were later validated in human subjects as illustrated in Fig. 3C and D. These quantitative insights into the expected hemodynamic effects of partial support contributed to selection criteria for the initial patients enrolled during the study of the Synergy device.

Another example of prospective use of simulation to predict effects of a hemodynamic device are provided by recent experience with an interatrial shunt device that is under evaluation for patients with heart failure and mildly reduced or preserved ejection fraction. Simulation was shown to reproduce the key features of left atrial pressure tracings recorded from a patient prior to and after closure of a preexisting congenital atrial septal defect (ASD) (Fig. 4), namely: (1) presence of large v-waves (in the absence of mitral regurgitation) and high mean left atrial pressure with the ASD closed and (2) normalization of relative a- and v-wave amplitudes and reduction in mean left atrial pressure with the ASD open. Second, it was predicted that an 8-mm interatrial shunt would create a left-to-right shunt fraction of ~1.3. Also, assuming an average baseline resting PCWP of 19 mmHg in the resting state, that resting PCWP was predicted to decrease by ~3 mmHg. In the subsequent pilot study, mean PCWP dropped by 5 mmHg, from 19 to 14 mmHg. Several other predictions are currently being evaluated in an ongoing clinical trial (the REDUCE LAP-HF Trial [A Study to Evaluate the DC Devices, Fig. 2. (A) Simulated pressure-volume loops predicted for a patient with chronic heart failure (solid lines) treated with either a left ventricle-to-aorta pump (dotted line) or a LA-to-aortic pump (dashed line). Qualitatively similar effects demonstrated in animal studies (B and C, respectively), as reported by Kono et al. 22 Ao, aorta; LA, left atrial; LVP, left ventricular pressure.
Simulation can be helpful in exploring the efficacy of an existing device for a new indication. For instance, mechanical circulatory support with a right ventricular assist device has been proposed for treating patients with pulmonary arterial hypertension and isolated right ventricular dysfunction. Issues related to safety and efficacy of such an approach have been highlighted by simulation and guidelines for establishing safe but effective right ventricular assist device flow rates were provided. These predications await clinical validation.

Predicting Results of Clinical Trials

The utility of modeling can, under special circumstances, extend into predicting the acute hemodynamic effects of surgical and interventional procedures, thus leading to the possibility of predicting therapeutic effects in a clinical trial. Two prominent examples are the prospective prediction of the results of studies of the Batista operation (for idiopathic cardiomyopathy) and the Dor operation (for ischemic cardiomyopathy). In both of these surgeries, a portion of the enlarged LV free wall and apex is removed with the intention of reducing wall stress. Simulations predicted, several years before clinical results, that the Batista operation would have a detrimental effect on pump function (Fig. 5), whereas the Dor procedure would have a neutral effect (Fig. 6). The detrimental effects of the Batista operation, in which weak but contractile muscle is removed, were shown to be due to more significant leftward shifts of the end-diastolic than end-systolic pressure-volume relationship, resulting in a reduction in net pump function (Fig. 5). The neutral effects of the Dor operation, in which akinetic scar is removed, were shown to be due to equal leftward shifts of the end-diastolic and end-systolic pressure-volume relationship, resulting in no net change in net pump function.

Fig. 3. (A, B) Model-predicted impact of left atrial-to-aorta MCS on CO and LV EDP as a function of device flow. (C, D) Corresponding observations in initial group of patients in which this form of MCS was tested. CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; MCS, mechanical circulatory support; PA, pulmonary artery.

Fig. 4. (A) Left atrial pressure tracing from a patient following closure of naturally occurring ASD. (B) Simulation results showing the same behavior, particularly as it relates to change in a- and v-waves. ASD, atrial septal defect.
change in pump function (Fig. 6). Both the predicted effects on hemodynamics (in terms of pressure-volume loops) and on clinical outcomes (in this case indexed by mortality) were confirmed in clinical studies of both the Batista\textsuperscript{32–34} and Dor operations.\textsuperscript{37–39}

Simulation-Guided Personalized Hemodynamic Therapy

One futuristic, untapped use of cardiovascular simulation is to help guide selection and optimization of device-based therapies for patients with hemodynamic abnormalities. Values of the model parameters can be adjusted to match the hemodynamic profile of a specific patient. The impact of a device, certain drugs, or certain types of surgical procedures on hemodynamics can then be predicted. With the growing number of approaches to treating acute and chronic right- and left-sided heart failure, there will be a need to develop means of matching each patient with the best therapy. This may not be able to be sorted out through traditional prospective clinical trials. Use of robust hemodynamic simulation-based predictions offers a logical approach. Some specific examples in which this approach could be helpful include: (1) identifying patients most likely to respond favorably to mitral repair/replacement; (2) identifying patients most likely to respond favorably to tricuspid repair/replacement; and (3) de-
deciding which therapy is best for a patient presenting with cardiogenic shock (ECMO vs direct left ventricle-to-aortic pumping versus biventricular support).

Model Limitations

Every model is subject to inherent limitations arising from underlying assumptions that are important to acknowledge when interpreting results. Basic assumptions of the model include load-independent time-varying elastance models of ventricular and atrial contraction and relatively simple lumped (0-order) network descriptions of the vascular beds. The limits of these assumptions have been detailed previously. More important are limitations from the lack of incorporating autonomic reflexes or means of long-term adaptation of simulation parameters. This renders the current embodiments of the model most relevant to predicting short-term effects. Incorporation of such feedback mechanisms while feasible necessarily introduce increasing large number of assumptions that have their own limitations. Finally, the utility of the presently described high-level simulation is most likely applicable to understanding basic physiological principles and effects of hemodynamic devices and surgical procedures and less applicable to understanding effects of specific drugs. Modeling of drug effects requires inclusion of models of receptor biology, intracellular signaling pathways, and patient-to-patient variability of receptor affinities; simulation of even acute drug effects can be very challenging.

Summary and Conclusions

Significant effort has been devoted over the past century to mathematically describe the individual components of the cardiovascular system and their interactions to yield detailed understanding of overall cardiovascular performance, particularly in the heart failure state. One philosophy of modeling builds the cardiovascular system from its fundamental building blocks of cross-bridges, ion channels, signaling pathways, and networks of branching elastic tubes. Another, simpler approach relies on high-level phenomenological descriptions of the vasculature and heart chambers. The latter approach is computationally simple and appears to provide adequate accuracy to explain a plethora of clinical physiology, heart failure pathophysiology, and therapeutics. Significant data have validated much of the behavior and predictions derived from this model, particularly on a conceptual level. Additional validation is required for application of this style of modeling to be used for detailed quantitative prediction of therapies, especially for its use to guide therapies in individual patients. For such an effort to be successful, there seems to be a need for reemphasis on hemodynamic education at every level of medical education; some novel teaching tools are now available (free of charge) to facilitate that effort. Application of cardiovascular models for heart failure clinical applications would be the ultimate reward for the more than a century of efforts that have brought us to the current state of knowledge.

Disclosures

Dr Doshi has received an educational grant from Abiomed. Dr Burkhoff is an employee of HeartWare International; on the speakers bureau for Abiomed; a consultant to Corvia Medical, Sensible Medical, and Impulse Dynamics; and founder of PVLoops LLC (the provider of the Harvi and Harvi-Student iPad applications). Harvi-Student has most of the features described in the text and is available for free download.

Appendix: Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2015.12.012.

References


