Review Article

Cardiovascular Simulation of Heart Failure Pathophysiology and Therapeutics

DARSHAN DOSHI, MD, MSc,[1] AND DANIEL BURKHOFF, MD, PhD[1,2]

New York, New York; Framingham, Massachusetts

ABSTRACT

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.[1] 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.[2] 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.[3] 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.[4] 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.[5,6] 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.[7] Suga and Sagawa introduced the *time-varying elastance* model to describe the time-dependent, load-

From the [1]Columbia University Medical Center/New York-Presbyterian Hospital, New York, New York and [2]HeartWare International, Framingham, Massachusetts.

Reprint requests: Daniel Burkhoff, MD, PhD, Columbia University Medical Center, 177 Fort Washington Ave, New York, NY 10032. Tel: +1 201 294 6081; Fax: (917) 398-1690. E-mail: Db59@columbia.edu (D. Burkhoff).

Manuscript received September 12, 2015; revised manuscript received November 23, 2015; revised manuscript accepted December 8, 2015.

See page 309 for disclosure information.

1071-9164/$ - see front matter

© *2016 Elsevier Inc. All rights reserved.*

http://dx.doi.org/10.1016/j.cardfail.2015.12.012

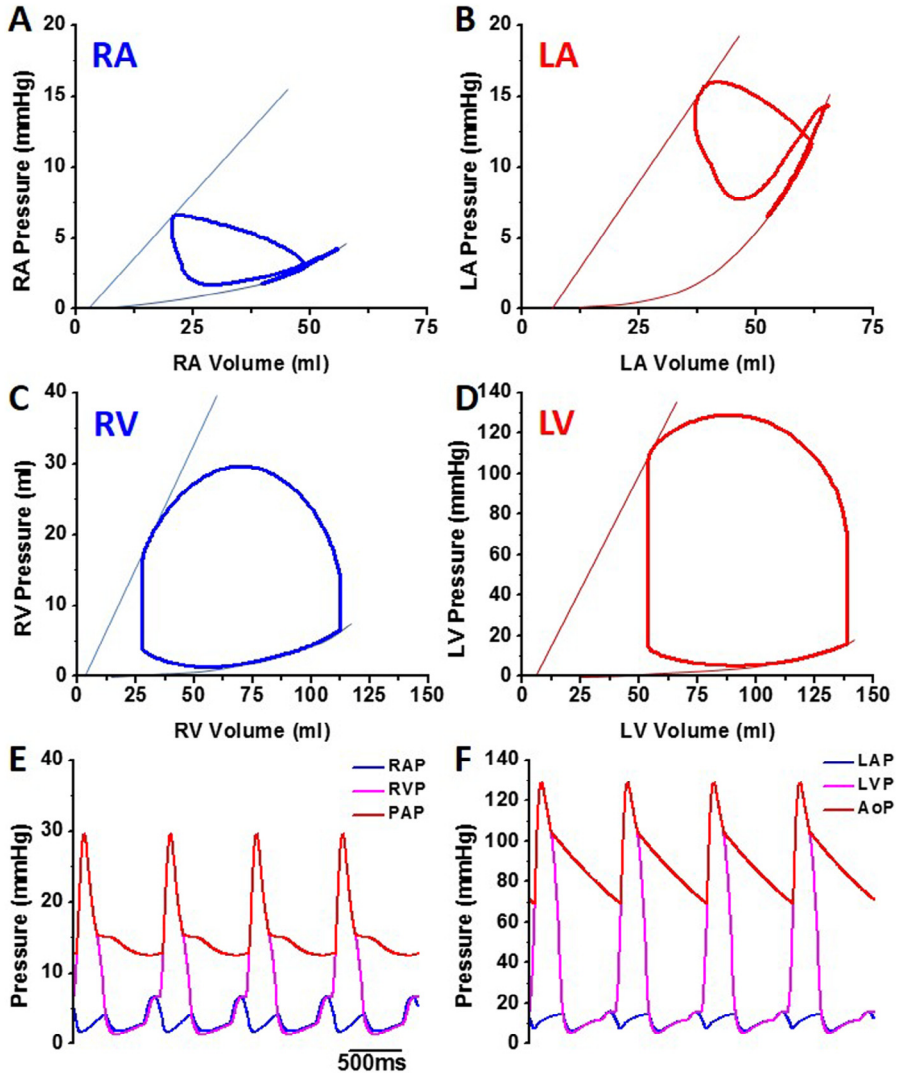

Fig. 1. RA, LA, RV, and LV pressure-volume loops generated from the cardiovascular model with normal parameter values (A–D). Time course of right- and left-sided pressures shown in E and F, respectively. LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular.

independent dynamics of atrial and ventricular contraction.[8,9] Sunagawa and colleagues[5] 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[6] (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.[10,11]

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

Clinical Observation	Reference	Supporting Data
Explained basic clinical observations:		
• Revealed the critical role of reflex-mediated venoconstriction in the generation of pulmonary congestion in the setting of LV dysfunction.	6	12,13
• Explains why patients with pulmonary hypertension can go into acute pulmonary edema with inhaled nitric oxide treatment.	14	12,13,15–17
• Clarification of the role of time constant of relaxation (τ) on LV end-diastolic pressure.	18	NA
• Clarification of the hemodynamic consequences of ventricular interdependence.	19	NA
• Explains the effects of different types of mechanical circulatory support devices on ventricular pressure-volume loops and energetics.	20	21–23
• Explains why the left ventricle can become overloaded when treating patients with ADHF with ECMO.	20	24,25
Predicting hemodynamic impact of device-based therapies and help guide patient selection:		
• Prospectively predicted impact of a new partial support device/strategy in patients with chronic heart failure.	26	26,27
• Prospectively predicted impact of an interatrial shunt on resting pulmonary capillary wedge pressure in patients with HFpEF.	28	29,30
Prospectively predicted results of clinical trials based on explanation of physiological principles:		
• Demonstrated that Batista operation would be detrimental to patients with idiopathic cardiomyopathy.	31	32–34
• Demonstrated that the surgical ventricular reconstruction (i.e., the Dor procedure) would have a neutral effect on LV function and mortality.	35,36	37–39

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 edema in the setting of acute left ventricular (LV) dysfunction[6]; (2) why pulmonary edema can occur with use of pulmonary vasodilator therapy in patients with pulmonary hypertension[14]; (3) the impact of changes in the time constant of relaxation at different heart rates[18]; and (4) the physiological significance of interventricular interactions in health and disease.[19] The first 2 examples have recently received independent validation from clinical data.[12,13,15–17] 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.[20,40] 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.[20] Experiments in animals and humans have confirmed the impact of some of these devices on LV pressure-volume loops[21,22,24,25]; 2 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.[20,22,40,41]

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.[20]

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

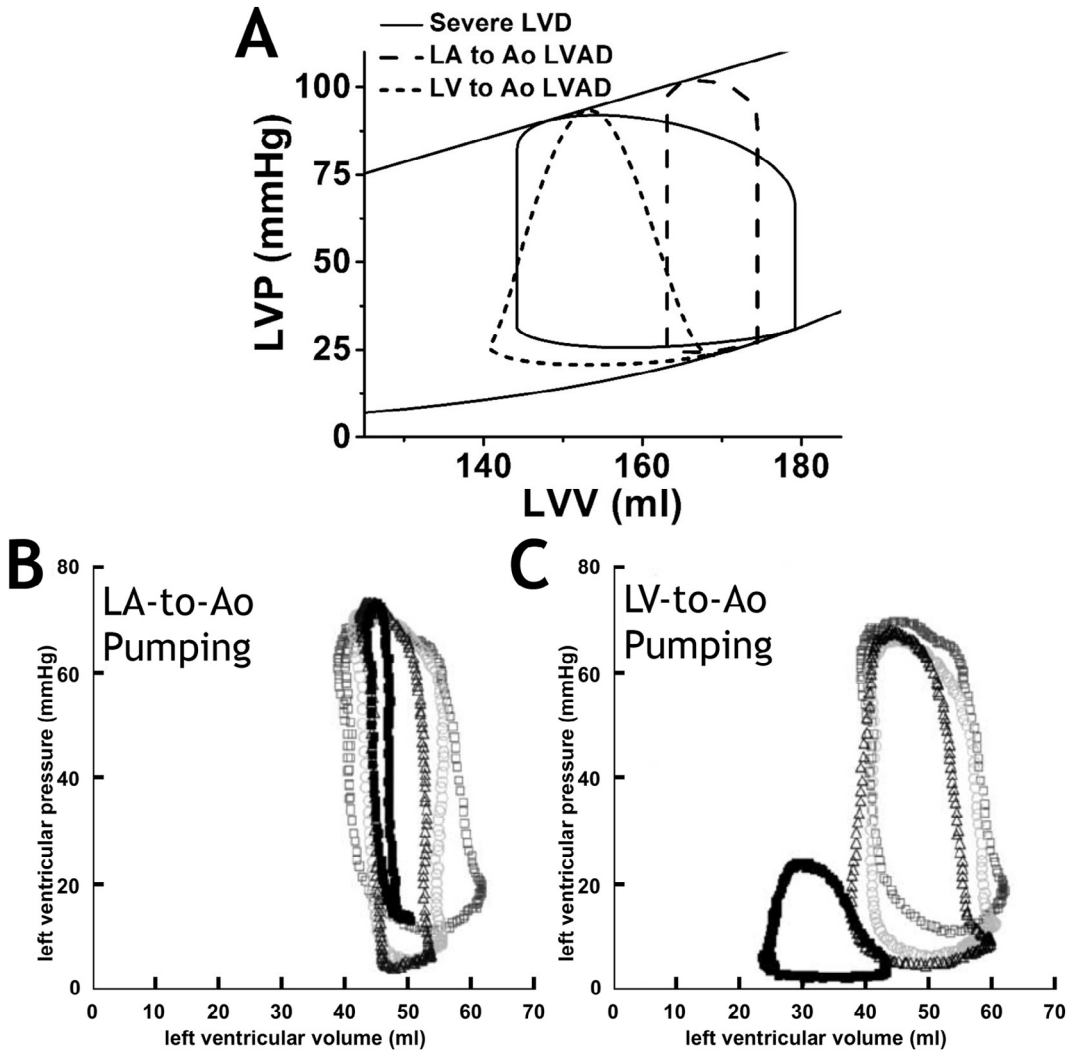

Fig. 2. (A) Simulated pressure-volume loops predicted for a patient with chronic heart failure (solid lines) treated with either a left ventricle-to-aorta pump (dotted line) or a LA-to-aortic pump (dashed line). Qualitatively similar effects demonstrated in animal studies (B and C, respectively), as reported by Kono et al.[22] Ao, aorta; LA, left atrial; LVP, left ventricular pressure.

Support) profile ≥4.[26] 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.[26] 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[26] (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[27] 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.[28] 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)[29] (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.[30] Several other predications are currently being evaluated in an ongoing clinical trial (the REDUCE LAP-HF Trial [A Study to Evaluate the DC Devices,

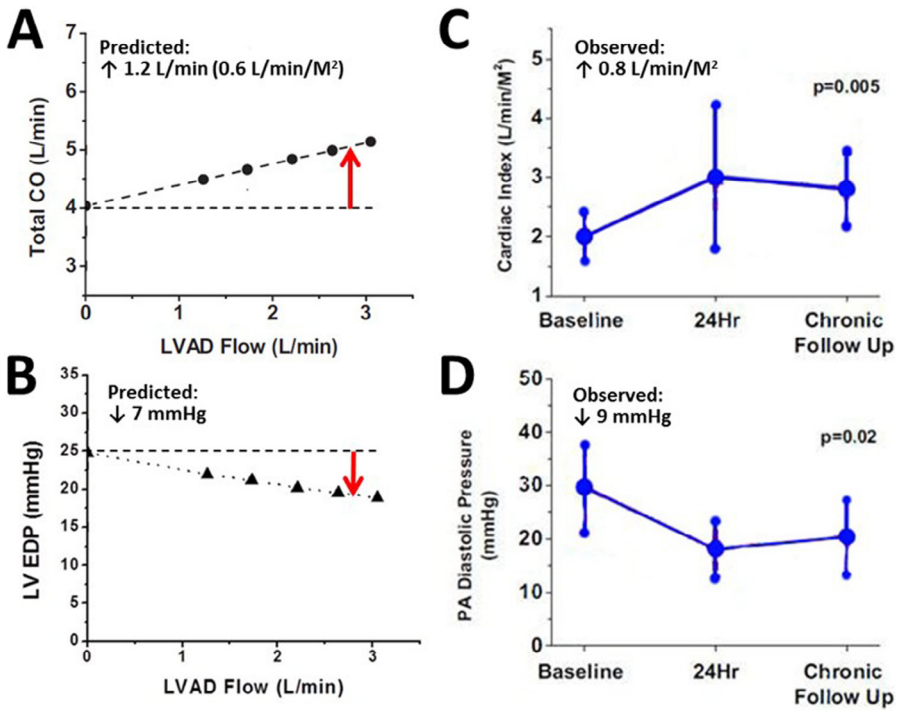

Fig. 3. (A, B) Model-predicted impact of left atrial-to-aorta MCS on CO and LV EDP as a function of device flow.[26] (C, D) Corresponding observations in initial group of patients in which this form of MCS was tested.[27] CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; MCS, mechanical circulatory support; PA, pulmonary artery.

Inc. IASD™ System II to REDUCE Elevated Left Atrial Pressure in Patients With Heart Failure], ClinicalTrials.gov identifier NCT01913613).

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.[42] These predications await clinical validation.

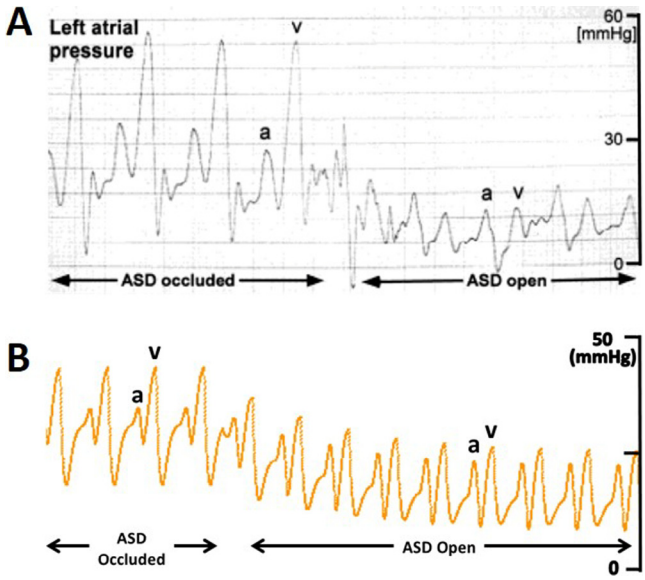

Fig. 4. (A) Left atrial pressure tracing from a patient following closure of naturally occurring ASD.[29] (B) Simulation results showing the same behavior, particularly as it relates to change in a- and v-waves.[28] ASD, atrial septal defect.

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 predicated, 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[35] (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

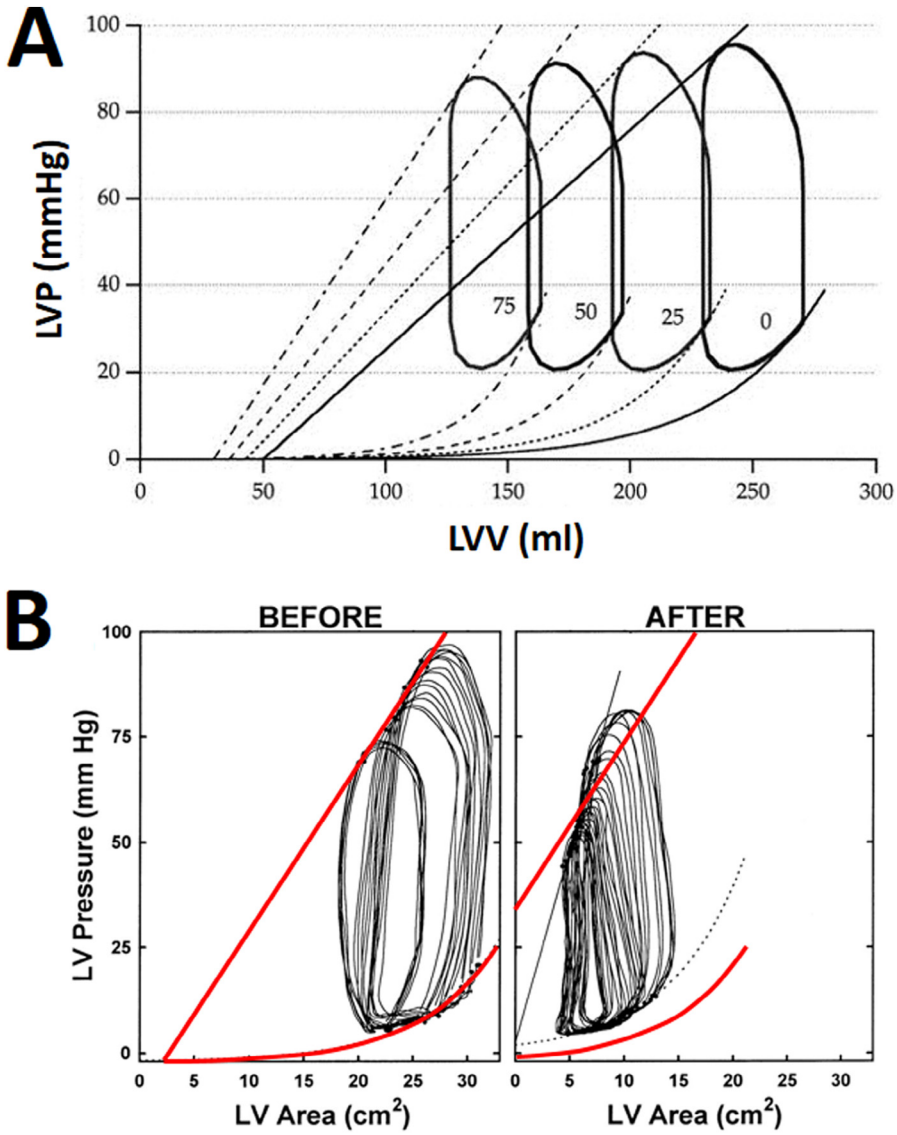

Fig. 5. Shifts of pressure-volume relations in response to excising different amounts of myocardium from the left ventricle of a patient with idiopathic cardiomyopathy. (A) The predicted leftward shift of the EDPVR is greater than the leftward shift of the ESPVR resulting in weaker heart.[35] (B) Predictions were confirmed by direct measurement in patients who underwent the procedure.[32] Red lines in the "before" loops (B) show the baseline ESPVR and EDPVR before surgery. The baseline ESPVR and EDPVR are transcribed and shifted onto the "after" pressure-volume loops to roughly align the ESPVR; as seen, the shift of the EDPVR is greater than the shift of the ESPVR so that there is a net reduction in LV pump function. EDPVR, end-diastolic pressure volume relationship; ESPVR, end-systolic pressure volume relationship; LV, left ventricular; LVP, left ventricular pressure; LVV, left ventricular volume.

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[32–34] and Dor operations.[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-

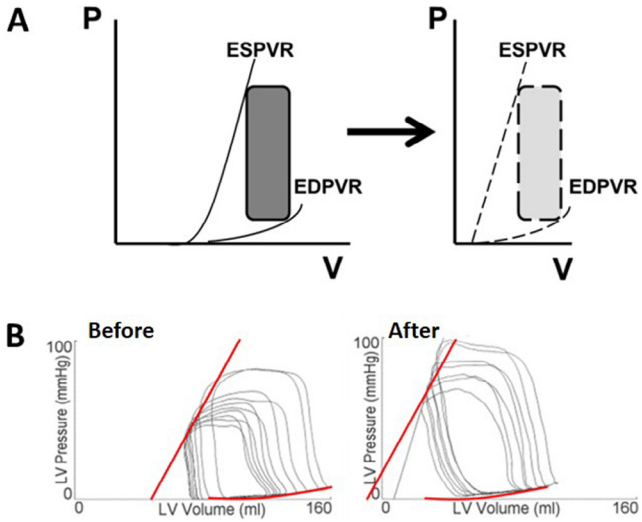

Fig. 6. Shifts of pressure-volume relations in response to excising different amounts of myocardium from heart with akinetic scar. (A) The leftward shifts of the EDPVR are predicted to be similar to those of the ESPVR, resulting in no significant change in overall ventricular contractile strength.[35] (B) These predictions were confirmed by direct measurement in patients who underwent the procedure.[37] Red lines in the "before" loops (B) show the baseline ESPVR and EDPVR before surgery. The baseline ESPVR and EDPVR are transcribed and shifted onto the "after" pressure-volume loops to roughly align the ESPVR; as seen, the shift of the EDPVR is very similar to the shift of the ESPVR so that there is no net change in LV pump function. EDPVR, end-diastolic pressure volume relationship; ESPVR, end-systolic pressure volume relationship; LV, left ventricular.

ciding 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.[43,44] 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[45] necessarily introduce increasing large number of assumptions that have their own limitations.[46] 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.[47,48] 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

1. Guyton AC, Coleman TG, Granger HJ. Circulation: overall regulation. Annu Rev Physiol 1972;34:13–46.
2. Smith NP, Hunter PJ, Paterson DJ. The cardiac physiome: at the heart of coupling models to measurement. Exp Physiol 2009;94:469–71.

3. Krenz GS, Linehan JH, Dawson CA. A fractal continuum model of the pulmonary arterial tree. J Appl Physiol 1992;72:2225–37.
4. Hester RL, Brown AJ, Husband L, Iliescu R, Pruett D, Summers R, et al. HumMod: a modeling environment for the simulation of integrative human physiology. Front Physiol 2011;2:12.
5. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245:H773–80.
6. Burkhoff D, Tyberg JV. Why does pulmonary venous pressure rise following the onset of left ventricular dysfunction: a theoretical analysis. Am J Physiol 1993;265:H1819–28.
7. Guyton AC. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 1955;35: 123–9.
8. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circ Res 1974;35:117–26.
9. Sagawa K. Editorial: the end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use. Circulation 1981;63:1223–7.
10. Maughan WL, Shoukas AA, Sagawa K, Weisfeldt ML. Instantaneous pressure-volume relationship of the canine right ventricle. Circ Res 1979;44:309–15.
11. Weimar T, Watanabe Y, Kazui T, Lee US, Moon MR, Schuessler RB, et al. Differential impact of short periods of rapid atrial pacing on left and right atrial mechanical function. Am J Physiol Heart Circ Physiol 2012;302:H2583–91.
12. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail 2011;4:669–75.
13. Dunlap ME, Sobotka PA. Fluid re-distribution rather than accumulation causes most cases of decompensated heart failure. J Am Coll Cardiol 2013;62:165–6.
14. Dickstein ML, Burkhoff D. A theoretical analysis of the effect of pulmonary vasodilation on pulmonary venous pressure: implications for inhaled nitric oxide therapy. J Heart Lung Transplant 1996;15:715–21.
15. Semigran MJ, Cockrill BA, Kacmarek R, Thompson BT, Zapol WM, Dec GW, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994;24:982–8.
16. Kieler-Jensen N, Ricksten SE, Stenqvist O, Bergh CH, Lindelov B, Wennmalm A, et al. Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. J Heart Lung Transplant 1994;13:366–75.
17. Bocchi EA, Bacal F, Auler Junior JO, Carmone MJ, Bellotti G, Pileggi F. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. Am J Cardiol 1994;74:70–2.
18. Hay I, Rich J, Ferber P, Burkhoff D, Maurer MS. Role of impaired myocardial relaxation in the production of elevated left ventricular filling pressure. Am J Physiol Heart Circ Physiol 2004;288:H1203–8.
19. Santamore WP, Burkhoff D. Hemodynamic consequences of ventricular interaction as assessed by model analysis. Am J Physiol 1991;260:H146–57.
20. Burkhoff D, Naidu SS. The science behind percutaneous hemodynamic support: a review and comparison of support strategies. Catheter Cardiovasc Interv 2012;80:816–29.
21. Bartoli CR, Giridharan GA, Litwak KN, Sobieski M, Prabhu SD, Slaughter MS, et al. Hemodynamic responses to continuous versus pulsatile mechanical unloading of the failing left ventricle. ASAIO J 2010;56:410–6.
22. Kono S, Nishimura K, Nishina T, Yuasa S, Ueyama K, Hamada C, et al. Autosynchronized systolic unloading during left ventricular assist with a centrifugal pump. J Thorac Cardiovasc Surg 2003;125:353–60.
23. Schreuder JJ, Maisano F, Donelli A, Jansen JR, Hanlon P, Bovelander J, et al. Beat-to-beat effects of intraaortic balloon pump timing on left ventricular performance in patients with low ejection fraction. Ann Thorac Surg 2005;79:872–80.
24. Rupprecht L, Florchinger B, Schopka S, Schmid C, Philipp A, Lunz D, et al. Cardiac decompression on extracorporeal life support: a review and discussion of the literature. ASAIO J 2013;59:547–53.
25. Combes A, Leprince P, Luyt CE, Bonnet N, Trouillet JL, Leger P, et al. Outcomes and long-term quality-of-life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. Crit Care Med 2008;36:1404–11.
26. Morley D, Litwak K, Ferber P, Spence P, Dowling R, Meyns B, et al. Hemodynamic effects of partial ventricular support in chronic heart failure: results of simulation validated with in vivo data. J Thorac Cardiovasc Surg 2007;133:21–8.
27. Meyns B, Klotz S, Simon A, Droogne W, Rega F, Griffith B, et al. Proof of concept: hemodynamic response to long-term partial ventricular support with the synergy pocket micro-pump. J Am Coll Cardiol 2009;54:79–86.
28. Kaye D, Shah SJ, Borlaug BA, Gustafsson F, Komtebedde J, Kubo S, et al. Effects of an interatrial shunt on rest and exercise hemodynamics: results of a computer simulation in heart failure. J Card Fail 2014;20:212–21.
29. Ewert P, Berger F, Nagdyman N, Kretschmar O, Dittrich S, Abdul-Khaliq H, et al. Masked left ventricular restriction in elderly patients with atrial septal defects: a contraindication for closure? Catheter Cardiovasc Interv 2001;52:177–80.
30. Sondergaard L, Reddy V, Kaye D, Malek F, Walton A, Mates M, et al. Transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel interatrial implant to lower left atrial pressure. Eur J Heart Fail 2014;16:796–801.
31. Dickstein ML, Spotnitz HM, Rose EA, Burkhoff D. Heart reduction surgery: an analysis of the impact on cardiac function. J Thorac Cardiovasc Surg 1997;113:1032–40.
32. Gorcsan J, Feldman AM, Kormos RL, Mandarino WA, Demetris AJ, Batista RJV. Heterogeneous immediate effects of partial left ventriculectomy on cardiac performance. Circulation 1998;97:839–42.
33. Schreuder JJ, Steendijk P, van der Veen FH, Alfieri O, van der Nagel T, Lorusso R, et al. Acute and short-term effects of partial left ventriculectomy in dilated cardiomyopathy: assessment by pressure-volume loops. J Am Coll Cardiol 2000;36:2104–14.
34. Starling RC, McCarthy PM, Buda T, Wong J, Goormastic M, Smedira NG, et al. Results of partial left ventriculectomy for dilated cardiomyopathy: hemodynamic, clinical and echocardiographic observations. J Am Coll Cardiol 2000;36:2098–103.
35. Artrip JH, Oz M, Burkhoff D. Left ventricular volume reduction surgery for heart failure: a physiologic perspective. J Thorac Cardiovasc Surg 2001;122:775–82.
36. Burkhoff D, Wechsler AS. Surgical ventricular remodeling: a balancing act on systolic and diastolic properties. J Thorac Cardiovasc Surg 2006;132:459–63.
37. Schreuder JJ, Castiglioni A, Maisano F, Steendijk P, Donelli A, Baan J, et al. Acute decrease of left ventricular mechanical dyssynchrony and improvement of contractile state and energy efficiency after left ventricular restoration. J Thorac Cardiovasc Surg 2005;129:138–45.
38. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360:1705–17.
39. Ten Brinke EA, Klautz RJ, Tulner SA, Verwey HF, Bax JJ, Schalij MJ, et al. Long-term effects of surgical ventricular restoration with additional restrictive mitral annuloplasty and/or coronary artery bypass grafting on left ventricular function: six-month follow-up by pressure-volume loops. J Thorac Cardiovasc Surg 2010;140:1338–44.
40. Burkhoff D. Device therapy: where next in cardiogenic shock owing to myocardial infarction? Nat Rev Cardiol 2015;12:383–5.
41. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of mechanical circulatory support. J Am Coll Cardiol 2015;66:2663–74.
42. Punnoose L, Burkhoff D, Rich S, Horn EM. Right ventricular assist device in end-stage pulmonary arterial hypertension: insights from a computational model of the cardiovascular system. Prog Cardiovasc Dis 2012;55:234–43.

43. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501–12.
44. Burkhoff D, Alexander J Jr, Schipke J. Assessment of windkessel as a model of aortic input impedance. Am J Physiol 1988;255:H742–53.
45. Burkhoff D, Sayer GT, Doshi D, Uriel N. Hemodynamics of mechanical circulatory support. J Am Coll Cardiol 2015;66:2663–74.
46. Hester RL, Iliescu R, Summers R, Coleman TG. Systems biology and integrative physiological modelling. J Physiol 2011;589:1053–60.
47. HARVI-Student: Introduction to Cardiac Mechanics and Hemodynamics (Version 1.0.2) [Mobile application software]. Available at: https://itunes.apple.com/us/app/harvi-student/id925178806?mt=8. 2015.
48. Lumens J, Delhaas T, Reesink KD, Arts T, Dassen W. Circadapt. http://www.circadapt.org/, accessed November 20, 2014. 2014.