Clinical Applications of Patient-Specific Models: The Case for a Simple Approach

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EDITORIAL

Clinical Applications of Patient-Specific Models: The Case for a Simple Approach

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Abstract

Over the past several decades, increasingly sophisticated models of the heart have provided important insights into cardiac physiology and are increasingly used to predict the impact of diseases and therapies on the heart. In an era of personalized medicine, many envision patient-specific computational models as a powerful tool for personalizing therapy. Yet the complexity of current models poses important challenges, including identifying model parameters and completing calculations quickly enough for routine clinical use. We propose that early clinical successes are likely to arise from an alternative approach: relatively simple, fast, phenomenologic models with a small number of parameters that can be easily (and automatically) customized. We discuss examples of simple yet foundational models that have already made a tremendous impact on clinical education and practice, and make the case that reducing rather than increasing model complexity may be the key to realizing the promise of patient-specific modeling for clinical applications.

Keywords Cardiac mechanics · Growth and remodeling · Computational modeling · Cardiology · Biomechanics

Introduction

A computational model is a concise, quantitative summary of how we think a system works and/or how we expect it to behave. Mechanistic models seek to represent the actual biologic and physical mechanisms that drive that system, while phenomenologic models seek to represent or predict its overall behavior without necessarily capturing the underlying mechanisms. Over the past several decades, mechanistic models of the heart have taught us much about how the cardiac action potential propagates, how the anatomic arrangement of the myofibers gives rise to ejection and torsion, and many other features of heart function. As their explanatory power has grown, these models have been increasingly used to predict the impact of diseases and therapies on the heart. Now, as we enter an era of personalized medicine, many envision patient-specific computational models as a powerful tool for personalizing therapy [1].

Yet the complexity of current state-of-the-art models poses an important challenge when contemplating their widespread clinical application. These models have naturally accumulated layers of detail and complexity as more data have become available, computing power has increased, and researchers have continued to innovate—which usually involves adding features rather than subtracting them. One challenge to applying these complex models in the clinic is that many of them require hours, days, or even weeks to run on sophisticated computing clusters. Although computing power does continue to increase, we contend that successful, widespread application of patient-specific models will require dramatically shorter run-times on the order of a typical clinic visit; otherwise, there will be no way to keep up with the constant flow of patients through a typical hospital or medical practice. Furthermore, model complexity poses fundamental challenges beyond the issue of computing time. Complex models contain a large number of parameters that must be fitted or customized to represent the features of a particular patient, while the requisite diagnostic data are scarce and relatively expensive to obtain. There are some model features—such as three-dimensional heart geometry—that can clearly be customized using routinely available methods, but this will incur substantial costs and likely require dedicated technicians or

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clinical engineers. The article by Trusty et al. in this issue [2] provides an excellent accounting of the workflow and personnel effort required for clinical application of a contemporary patient-specific vascular model, something we would welcome in every patient-specific modeling paper. And there are other model features—such as the stress–strain behavior of the myocardium—that cannot be directly measured, but instead must be identified through parameter fitting approaches that become less reliable as the number of parameters increases.

Here, we propose that while the evolution of mechanistic models described above has provided important insight into how the heart works and responds to diseases and therapies, early successes in applying patient-specific heart models in the clinic are likely to arise from a very different approach: relatively simple, fast, phenomenologic models with a small number of parameters that can be easily (and automatically) customized. Such approaches are likely to rely on decades-old models such as the Windkessel model of the arterial circulation or the time-varying elastance model of myocardial contraction. Here, we provide a few examples of simple yet foundational models that have already made a tremendous impact on clinical education and practice. Then, we discuss how these and other simple models could enable patient-specific modeling moving forward. In particular, we propose that reducing rather than increasing model complexity may be the key to realizing the promise of patient-specific modeling for clinical applications.

Success Stories

The Windkessel

Around 1900, pioneering physiologist Otto Frank formalized and popularized the conceptual model that still underlies our understanding of arterial physiology today: the compliance of the large arteries buffers the pulses of flow emerging from the left ventricle during systole, while small arteries and arterioles determine the net resistance to flow through the arterial tree [3, 4]. A family of quantitative models that represent this idea using capacitors, resistors, and other basic circuit elements became known as Windkessel models, after the German word for a reservoir used to smooth pulsatile flow in early fire engines [5]. As detailed in an excellent review by Westerhof et al., these Windkessel models have had an enormous impact on our understanding of cardiovascular physiology, on medical and physiology education, and on clinical practice [5].

One key impact of Windkessel models was the realization that both compliance of the large arteries and resistance of the small arteries influence ventricular–vascular coupling and clinically measured arterial blood pressures. For example, even without a quantitative model it was easy to envision that impaired vasodilation in resistance vessels could produce hypertension by increasing the amount of pressure the heart must generate to push flow through the arterial network. But Windkessel models suggested that vascular stiffening due to aging or diabetes would also increase pulse pressure (the difference between systolic and diastolic arterial pressure), which is now recognized as an independent risk factor for cardiovascular disease [6, 7]. The ability of Windkessel models to predict the quantitative, dynamic relationships between cardiac output and arterial pressure in real time enabled new diagnostic tools. For example, as reviewed by Truijen et al., fitting a Windkessel model to a measured arterial pressure waveform—which can be measured noninvasively using commercially available monitors—allows continuous measurement of cardiac output [8]. This technology has been applied clinically to a wide range of problems, from monitoring fluid status during surgery to diagnosing syncope [8].

Another advantage of Windkessel models is that they provide a simple way to simulate the properties of the arterial system when studying cardiac physiology. An isolated heart connected to a single outflow tube follows a completely unphysiologic pressure–volume path, while adding a simple compliance chamber produces reasonably physiologic pressure–volume loops, facilitating experimental studies of ventricular mechanics and energetics under controlled conditions. Similarly, the compartmental models described below must be connected to at least a minimal two-element Windkessel model (a capacitor and resistor in parallel) to generate realistic pressure–volume behavior. The fact that Windkessel models provide such an economical representation of fundamental arterial properties has motivated their use to represent outflow boundary conditions across a wide range of models, including state-of-the art, anatomically and geometrically detailed finite-element models of the heart [9] and complex computational fluid dynamics models of the aorta [10] and coronary arteries [11]. In fact, this approach is so pervasive that both Chiastra et al. [12] and van Bakel et al. [13] reference the use of Windkessel models to specify outflow boundary conditions in their articles in this issue.

Time-Varying Elastance

Model Overview

Otto Frank was also an early pioneer in analyzing pressure–volume relationships in the heart [3, 4]. Plotting the internal pressure of the left ventricle (LV) against its volume produces a loop with many interesting properties; Kiichi Sagawa and his colleagues at Johns Hopkins University popularized pressure–volume analysis in the 1970s and 1980s and developed an extremely influential yet simple model of LV pump function called the time-varying elastance model [14, 15]. The basis for their model was the experimental observation that when they connected LV pressure–volume points collected at

the same relative times during multiple contractions over a range of loading conditions, those points fell on straight lines whose slope gradually increased, peaked at the end of ejection, and then decreased again (Fig. 1).

Mathematically, the time-varying elastance model is embodied in a single equation: $P(t) = E(t) * [V(t) - V_0]$. Conceptually, this equation describes a gradual transition of the LV from a relaxed state during diastole to a maximally contracted state at end-systole, followed by a gradual relaxation. The time-varying elastance model is phenomenologic, relying on the experimentally measured function $E(t)$. Nevertheless, it has proven remarkably influential and versatile because that function turned out to be stable over a wide range of loading conditions. Thus, this model not only allows accurate prediction of the time course of LV pressure generation given known volumes (or vice versa), it can also be coupled to models of the circulatory system to understand ventricular–vascular coupling and to predict dynamic responses to drugs or hemodynamic interventions in just a few seconds.

While $E(t)$ is remarkably independent of preload and afterload, it changes whenever the intrinsic properties of the myocardium or the LV geometry change. In some ways, this feature has also proven useful; for example, E_{max}—the peak value of E(t)—provides a useful index of contractility that varies with administration of drugs that alter force of contraction in individual myocytes. However, care must be taken to limit predictions using a given $E(t)$ curve to settings where that function remains appropriate.

Model Impact

Suga and Sagawa's pressure–volume framework for analyzing cardiac function is now pervasive in medical education, included in most physiology and heart disease textbooks. Time-varying elastance and in particular the end-systolic pressure–volume relationship (ESPVR) thus provide a conceptual model for physicians throughout the world as they evaluate patients and weigh treatment options. With the advent of methods for measuring pressure–volume loops in patients [16, 17], direct measurement of the ESPVR has also proved useful for guiding clinical decisions. For example, Kass and Maughan showed that measuring the ESPVR in the cardiac catheterization laboratory helped them predict the response of individual patients with dilated cardiomyopathy to vasodilator therapy [18]. Ehsani et al. used systolic pressure–volume ratios to show that exercise training could improve LV performance in patients with clinically significant coronary artery disease [19].

Time-varying elastance and the ESPVR also proved useful in better understanding the factors that determine heart performance in patients with various forms of heart disease. For example, Kass et al. confirmed that LV hypertrophy increases E_{max}, highlighting the importance of considering chamber geometry when assessing LV function in the setting of hypertrophy or remodeling [17]. A decade later, Kass et al. used shifts in the ESPVR to examine the effect of different pacing strategies in patients with dilated cardiomyopathy and a widened QRS on intrinsic LV contractile function [20], contributing to the development of effective cardiac resynchronization therapy (CRT) strategies. Metrics of ventricular–vascular coupling related to the time-varying elastance model also have prognostic value in some settings: Obokata et al. recently reported that the ratio E_a/E_{es} had incremental prognostic value over ejection fraction or other echo measures for adverse outcomes in dialysis patients [21].

Perhaps most relevant to this review, simple computational models that employ the time-varying elastance model to represent LV and/or RV contraction and a combination of resistors and capacitors to represent the circulatory system (see Section 2.1 above) have proven remarkably powerful in understanding complex aspects of heart function and ventricular–

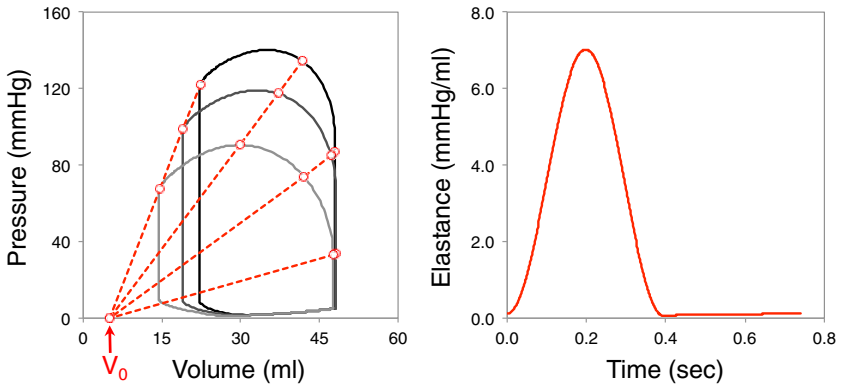

Fig. 1 Illustration of the concept of time-varying elastance, generated using a compartmental model of the canine left ventricle coupled to a circuit model of the circulation. Varying simulated arterial resistance generates a series of pressure–volume loops for the left ventricle with different peak pressures and stroke volumes (left panel, black/gray lines). Connecting pressure–volume points acquired at the same times across these loops produces a family of lines with a variable slope (left panel, dotted red). The slope of these lines $E(t)$ increases, peaks at end systole, and then decreases again (right panel)

vascular coupling and even in prospectively predicting the effects of novel interventions. For example, Santamore and Burkhoff [22] showed that pressure generation by the left ventricle substantially enhances contractility (E_{max}) of the right ventricle, a finding that has influenced therapies ranging from cardiac resynchronization therapy (CRT) to left ventricular assist devices (LVADs). Dickstein et al. predicted as early as 1997 [23, 24] that the Batista operation would produce limited improvement in patients with idiopathic heart failure because gains in systolic function would be offset by losses in diastolic function, a prediction that proved prescient [25, 26].

As will be discussed in more detail below, the fact that these simple models of the ventricles coupled to a circulation can run in real time on any modern desktop or laptop computer represents an important advantage for some applications. Such models have already been used extensively as simulators for medical education [27–30]. Real-time simulation potentially allows clinicians to screen therapeutic options and observe responses immediately, rather than waiting days or weeks for a simulation result. Furthermore, as the modeling community moves toward simulating long-term responses such as LV growth and remodeling over months and years, only very fast models will be able to make predictions quickly enough for clinical decision support.

Compartmental Models of Ischemia: As Simple as Possible, But Not Simpler

Model Overview

As discussed above, the slope of the end-systolic pressure–volume relationship (ESPVR) has proven to be a useful index of ventricular contractility. Thus, one might expect that acute myocardial infarction should reduce the slope of this relationship (E_{max} or E_{ES}). Yet Sunagawa et al. showed experimentally that myocardial infarction had little effect on E_{ES}, instead shifting the intercept (V_0) of the ESPVR in proportion to the size of the infarct [31]. Even more remarkably, they were able to replicate this behavior using an extremely simple model that represented the left ventricle using two compartments: a normally contracting compartment described by the time-varying elastance model, and a passive ischemic compartment where pressure and volume were related according to the end-diastolic pressure–volume relationship (EDPVR) at all times.

This model is a wonderful example of the adage that a model should be as simple as possible, but not simpler. Ignoring the complex biology that underlies myocardial ischemia and the complex three-dimensional mechanics of regional ischemia, Sunagawa's simple model nevertheless accurately predicts measured pressure–volume behavior over a wide range of loading conditions and infarct sizes. However, this accuracy depends entirely on one improvement over the original time-varying elastance model. While time-varying elastance represents pressure–volume behavior using a series of straight lines, Sunagawa's compartmental model of ischemia recognizes the nonlinearity of the EDPVR, using an exponential function rather than a straight line to represent the passive compartment. As shown in Fig. 2, this one change is the difference between matching the experimental data beautifully or making fundamentally flawed predictions.

Model Impact

Sunagawa's work and other conceptually similar compartmental models have had an important impact on our understanding of the clinical physiology of myocardial infarction and potential therapies. Bogen et al. used a slightly more complex model that exhibited similar pressure–volume behavior to explore the effect on pump function of gradual stiffening of the infarct due to replacement of necrotic myocardium by collagenous scar [32]. Bogen's model produced a fundamental insight about the impact of infarct stiffness on LV function that has been repeatedly confirmed by more sophisticated computational models and experiments: stiffening the infarct improves systolic function by limiting bulging of the infarct, but impairs diastolic function by restricting filling, producing no overall improvement in pump function. This prediction has received renewed attention in recent years as researchers have sought to design synthetic or bioengineered patches, injectable biomaterials, and other interventions that can improve post-infarction function [33, 34].

As another example, Burkhoff and Tyberg challenged the conventional wisdom that reduced LV systolic performance is sufficient to trigger elevated pulmonary pressures and pulmonary edema seen clinically in acute heart failure following myocardial infarction [35]. Using a compartmental model of the ventricles connected to a circuit model of the circulation, they showed that ventricular dysfunction alone causes little change in pulmonary pressures. In fact, of the several hemodynamic compensatory mechanisms that can be triggered by baroreceptor-mediated activation of the sympathetic nervous system, only venoconstriction increased simulated pulmonary pressures to levels associated clinically with pulmonary edema. This model prediction has gained new importance with the recent advent of continuous hemodynamic monitoring in heart failure patients, which suggests that sympathetic control of venous reservoir volume can trigger decompensations resulting in heart failure [36].

One-Fiber Model

Model Overview

One important drawback of compartmental models is that they do not explicitly represent force–length and force–velocity behavior of the myocytes or myofibers, a feature that can be important when modeling drugs or mutations in sarcomeric

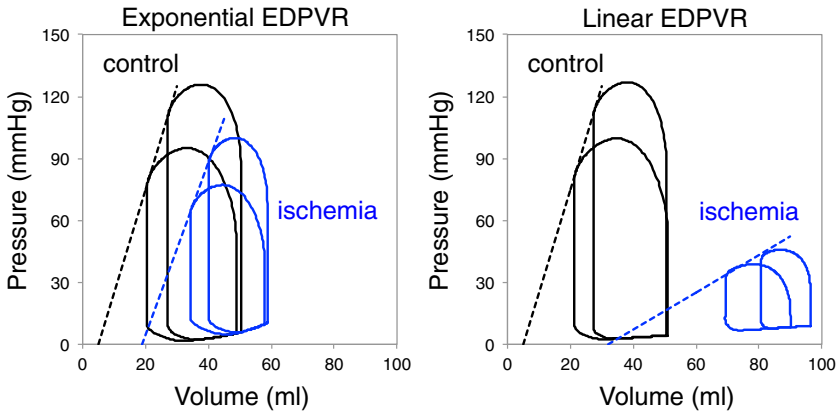

Fig. 2 Simulation of acute ischemia using Sunagawa's two-compartment model of the ischemic left ventricle coupled to a circuit model of the circulation. Varying arterial resistance to construct ESPVRs (dotted lines) predicts a rightward shift in the ESPVR but little change in slope between control (left panel, black loops) and simulated ischemia affecting 20% of the LV (left panel, blue loops), matching Sunagawa's experimental observations [31]. However, modeling the passive properties of the myocardium using a linear EDPVR instead of an exponential relationship leads to completely unphysiologic predictions of the impact of the same 20% ischemic region (right panel)

proteins that affect myofilament mechanics. The most common approach to integrating fiber-level behavior to predict overall heart function and mechanics is to employ finite-element (FE) models that incorporate the 3D geometry and fiber structure of the heart. As noted above, for patient-specific applications, it is certainly possible to obtain, segment, and employ patient-specific geometries from MRI or another clinical imaging modality. However, patient-specific measurement of myofiber anatomy remains more difficult, and multiple simulations suggest that many predictions of FE models are particularly sensitive to even small errors or uncertainty in fiber orientation. For example, Pluijmert et al. recently investigated the sensitivity of cardiac function to geometry and myofiber orientation in a biventricular (BiV) FE model and found that an average change in myofiber orientation of just 8° produced nearly 20% increases in predicted regional myofiber work and global pump work [37]. In a finite-element model of diastolic mechanics of the rat ventricle, Holmes showed that a 10° shift of the transmural fiber distribution resulted in a 15-fold change in the ratio of material parameters in the fiber and cross-fiber directions required to fit experimental data from rats [38].

The one-fiber model proposed by Arts et al. provides an interesting alternative approach for integrating fiber-level mechanics to predict global ventricular behavior [39]. Building on prior studies showing that measured fiber strains and calculated fiber stresses are nearly constant across the wall of a normal left ventricle, Arts assumed homogeneity of fiber stress and strain and derived simple analytic formulas to relate these quantities to LV pressure and volume, using the physical principle of conservation of energy.

Model Impact

Clinical applications of the one-fiber model include studies on ventriculo-vascular interactions in middle-aged adults without cardiovascular disease [40] and patients with hypertension [41], and ventriculo-valvular interactions in patients with severe mitral regurgitation undergoing mitral repair [42]. Although originally developed to relate myofiber mechanics and global pump function under the assumption of regional homogeneity of stress and strain, the one-fiber principle was recently used by Walmsley et al. to model regional heterogeneity of myofiber mechanics in asynchronously activated hearts [43]. Simulated LV strain patterns showed good quantitative and qualitative agreement with regional strain data measured in paced dog hearts, and the model also predicted observed pacing-induced heterogeneity of regional myofiber work. Integrated in the closed-loop CircAdapt model of the heart and circulation, this model allows real-time simulation of cardiovascular tissue mechanics and hemodynamics (www.circadapt.org). Recently, it was used to devise a novel diagnostic index, called the systolic stretch index, which enables noninvasive quantification of the combined electromechanical substrate responsive to cardiac resynchronization therapy (CRT). In a clinical study, this index proved to be predictive of clinical outcome after CRT in a cohort of 191 CRT candidates, even in patients with an uncertain indication for CRT using the conventional ECG criteria [44]. In another study, Mast et al. used the CircAdapt model to characterize the pathophysiological substrates underlying regional right ventricular deformation abnormalities in subjects carrying a desmosomal mutation associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) [45]. This study led to the clinically relevant insight that half of the subclinical ARVC mutation carriers exhibit mechanical abnormalities related to subtricuspid contractile dysfunction before development of detectable electrical abnormalities, challenging the conventional staging criteria for this disease [46]. In the light of the growing need for validated and time-efficient cardiac modeling approaches for patient-specific simulation in a clinical

setting, variants of the one-fiber model may prove to be a particularly useful middle ground between compartmental and finite-element models.

Opportunities to Make a Clinical Impact

Phenomenologic Growth Models

Most published computational models of therapeutic interventions seek to determine the acute effects of a proposed treatment. These studies ask important and potentially valuable questions such as how injecting polymers into a myocardial infarct [47], placing a pacemaker lead in a particular location [48, 49], or performing radiofrequency ablation to treat atrial fibrillation [50] will alter cardiac function. Yet in most cases, the clinician cares most about something these models cannot predict: what will happen in the months or years following the treatment? Will heart failure progress or regress? Will the arrhythmia recur? Thus, one of the most exciting frontiers in cardiovascular biomechanics is the development of models that predict growth and remodeling of the heart and blood vessels. Such models offer the tantalizing possibility of making long-term predictions that can guide therapy in individual patients.

Some of the most successful models of cardiac growth are phenomenologic rather than mechanistic [51–54]. As one example, a simple set of equations developed by Kerckhoffs et al. [54] correctly predicted patterns of growth observed during experimentally induced aortic stenosis [54], mitral regurgitation [54], and dyssynchrony [55]. These phenomenologic growth equations typically allow rapid calculation of the current predicted rate of growth from current stresses or strains, but when implemented in complex FE models the need to simulate weeks or months of growth with step sizes of hours or days multiplies the computational demands many fold: Kerckhoffs' original simulations of aortic stenosis and mitral regurgitation required roughly 3 weeks on a computing cluster to simulate 1 month of left ventricular remodeling [54].

We consider this an excellent potential application for the simpler LV and circulatory models discussed above. Combining phenomenologic growth equations with compartmental or single-fiber models of LV mechanics might offer the ability to predict long-term responses fast enough to inform clinical decisions for individual patients. In this issue, Witzenburg et al. take exactly this approach, connecting a compartmental model of the ventricles and circulation to a variant of the Kerckhoffs growth equations to simulate months of remodeling in just a few minutes on a standard desktop [56].

Customizing Models Using Adaptation Rules and Atlases

In general, a patient-specific heart model is intended to represent the most likely status of a patient's heart and its interaction with the surrounding large vessels. In a conventional clinical setting, the quantitative information that is available for model parameter estimation is often scarce. Therefore, deciding how many adjustable model parameters to employ requires seeking a workable compromise wherein the complexity (number of parameters) is large enough to describe the (patho)physiological problem of interest and small enough to easily and reliably parameterize using the available clinical information. The models discussed above are exemplary for the fact that much efficiency can be gained by application of physical, physiologic, and pathophysiologic principles using a relatively small number of degrees of freedom (i.e., unknown model parameters).

Currently, there is a tendency in patient-specific modeling to envision the acquisition of ever more information by addition of emerging technologies—such as diffusion tensor imaging for identifying myofiber directions—to conventional clinical evaluations. Nevertheless, for reasons of both cost efficiency and minimizing impact on the patient, it is important to employ scans and other measurement techniques for obtaining patient-specific data with utmost efficiency. One potentially powerful alternative is to use validated atlas-based or rule-based approaches to estimate features such as myofiber orientations rather than measuring them directly. As reviewed by Gilbert et al. in this issue [57], atlas-based approaches project the geometry of an individual heart onto a database reflecting the variability in shape, size, and other features across a population of previously imaged hearts. If fiber anatomy is closely correlated with heart geometry, then the projection of an individual geometry onto a database can also provide a good estimate of that heart's fiber anatomy [58]. Elsewhere in this issue, Lee et al. discuss the use of rule-based methods for determining fiber anatomy in simulations of cardiac resynchronization therapy [59].

Another powerful but underused way of reducing input parameter uncertainty is to model the process of structural adaptation that produced the current fiber orientation or other feature of interest. For example, Arts et al. proposed a set of fiber adaptation rules that automatically produced realistic transmural myofiber distributions in a computational model, even when the initial fiber geometry was unphysiologic [60]. Models incorporating these rules were able to match the altered fiber structure and mechanics of situs inversus totalis hearts [61], and have been used to estimate the effect of geometric changes on fiber anatomy [37]. Similarly, the CircAdapt framework [62] and models of blood pressure control [63] have been used to estimate

the evolution of loading conditions on the ventricle during hemodynamic overload. When integrated in patient-specific modeling schemes, such models can provide repeatable and consistent estimates of parameters for which patient measurements are unavailable or too costly to acquire, by applying a small number of underlying homeostatic rules and principles.

But Surely There Must Be Limits?

We have focused here on the successes of simple models and tried to identify some areas where their application might advance the practical application of patient-specific modeling. Yet every model has limitations, and when developing and testing models for clinical applications, it will be essential to clearly identify in what settings each model is known (and not known) to be valid. In particular, while phenomenologic models are often fast, they are usually based on measured relationships that only hold under certain conditions. Some of these have mentioned in passing above. For example, the classic three-element Windkessel model offers a linear description of arterial input impedance, while the arterial wall tissue is known to have nonlinear stress–strain behavior. As a result, the Windkessel parameter values (i.e., wave impedance, compliance, and peripheral resistance) have to be re-estimated after each change of hemodynamic load to the modeled system. This can be seen as an important drawback in the light of patient-specific modeling of therapy effects. As another example, the time-varying elastance model holds over a wide range of hemodynamic conditions (preload and afterload), but whenever intrinsic contractility or geometry change, the $E(t)$ function must be revised accordingly. Similarly, Sunagawa's compartmental model of ischemia only works when the nonlinear properties of ischemic myocardium are correctly represented, and these properties need to be adjusted if the model is applied to patients with chronic infarcts. The one-fiber model was originally developed assuming that fiber stress and strain are homogeneous; even if this is true in the normal heart, it might not hold in settings like dyssynchrony or during transient growth responses following a hemodynamic perturbation. Ultimately, patient-specific models must be employed as carefully as any other diagnostic tool or medical treatment—they must be specifically validated for their predictive power in well-defined trials and applied only in the specific settings in which they were validated.

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Compliance with Ethical Standards

Conflict of Interest J.W.H. declares that he has no conflict of interest. J.L. has served as a consultant to Medtronic.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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