Editorial

Cardiac Simulation to Personalize Cardiac Resynchronization Therapy
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Personalized medicine of heart failure patients has become the holy grail of ongoing research. Identification of responders to medical or device therapy before initiation of the therapy would be ideal to improve survival and reduce cardiovascular events.1 Particularly, in the field of heart failure, selection of patients who will benefit from cardiac resynchronization therapy (CRT) has attracted much attention. Left ventricular (LV) dyssynchrony, extent and location of myocardial scar, and position of the LV pacing lead, among other clinical variables, have shown to be strong determinants of the therapeutic response and outcomes.2,3 Although current guidelines do not include imaging criteria to select patients for CRT,4,5 many centers use imaging modalities (echocardiography, magnetic resonance imaging, computed tomography, and nuclear imaging) to select the patients and tailor the therapy to optimize the clinical results. Echocardiography is the imaging technique of first choice because of its versatility and widespread availability. It can provide information on LV dyssynchrony and site of latest mechanical activation and indicate the regions with a significant extent of myocardial scar tissue. Magnetic resonance imaging using late gadolinium enhancement provides information on scar extent and location with superior spatial resolution over echocardiography and can depict cardiac venous anatomy with similar accuracy as with computed tomography. Initial experience with fusion imaging, overlaying magnetic resonance imaging data on myocardial scar location, and cardiac venous anatomy onto fluoroscopy or positron emission tomography and data on myocardial scar location, and cardiac venous anatomy, and computed tomography, can depict cardiac venous anatomy with similar accuracy as with computed tomography. Initial experience with fusion imaging, overlaying magnetic resonance imaging data on myocardial scar location, and cardiac venous anatomy onto fluoroscopy or positron emission tomography and computed tomography have been developed to tailor CRT delivery and avoid LV lead placement in areas of scar tissue.6,7 Despite these efforts, the rate of nonresponse to CRT remains unchanged, and the use of sequential imaging may lead to increased costs. In an ideal situation, the information obtained from each patient could be used to generate a cardiac model that permits accurate prediction of the effects of CRT for each individual.

Cardiac modeling and simulation technologies have increased our knowledge on heart failure pathophysiology and the effects of CRT on cardiac structure and function.8 Based on the pioneering modeling work of Hodgkin and Huxley,9 the initial models developed in the 1960s, trying to unravel the electrophysiological properties of the cardiac cells, have evolved in the last decades to models with sufficient patient customization that allow for personalized treatment.8 For example, electrocardiographic imaging is based on electrophysiological models that reconstruct the cardiac electric activity on the epicardial surface.10 From a multielectrode vest, 224 body surface ECGs are combined with the anatomic information obtained from computed tomography, displaying the body surface potentials on a subject-specific torso and ventricular epicardial geometry. This cardiac modeling technology permits characterization of ventricular activation sequence in heart failure patients with ventricular conduction disturbances. In 33 patients treated with CRT (18 with left bundle branch block [LBBB] QRS morphology and 15 with nonspecific intraventricular conduction disturbance), Ploux et al11 showed that electrocardiography imaging permitted differentiation of several LV activation patterns that were related with therapy response. Patients with LBBB configuration showed homogeneous patterns of LV activation with a single anterior or lateral right ventricular breakthrough site and no epicardial breakthrough in the left ventricle, which was activated passively from the right ventricle. In addition, the propagation of the action potential was impaired by the presence of lines of slow conduction oriented from base to apex and located at the anteroseptal, anterolateral, posterolateral, and posteroseptal surfaces. In contrast, in patients with nonspecific ventricular conduction delay, the breakthrough could be observed in the left ventricle, and the activation sequence was heterogeneous with lines of slow conduction shorter and of variable distribution in the left ventricle compared with their counterparts. As a result, the LV total activation times and ventricular electric uncoupling, defined as the difference between mean LV and right ventricular activation times, were longer in patients with LBBB QRS morphology compared with patients with nonspecific ventricular conduction delay (115±21 versus 91±34 ms, P<0.03; and 72±12 versus 40±22 ms, P<0.001; respectively). Particularly, a ventricular electric uncoupling of ≥50 ms predicted response to CRT with a sensitivity and specificity of 90% and 82%, respectively, independently of the QRS morphology. However, electrophysiological models focus only on the electrophysiological aspects of the heart and do not integrate the function and structure of the heart. Eventually, it would be interesting to predict with cardiac modeling an improvement in cardiac structure and function with heart failure therapies.

See Article by Lumens et al

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The electromechanical models instead characterize the electric propagation and mechanical deformation of the left ventricle. From the initial models in the early 1970s, the technology has evolved to finite element modeling, which has been increasingly adopted in the study of LV mechanics in physiological and pathological conditions. These models take into consideration the myocardial fiber arrangement and direction, as well as the LV geometry and remodeling, which affect the electric and mechanical properties of the left ventricle. Diffusion tensor magnetic resonance imaging has demonstrated an increase of the epicardial and endocardial fiber angles of failing hearts, for example. In addition, anatomic models of LV geometry and fiber architecture can be coupled with regional myocardial mechanics to study the effects of pacing. In this issue of *Circulation: Cardiovascular Imaging*, Lumens et al used computer simulations to characterize mechanical discoordination patterns arising from electric activation delay, LV regional differences in contractility, and regional myocardial scar and proposed a novel systolic stretch index as a measure of cardiac dyssynchrony. Using the CircAdapt computational model, local ventricular myofiber mechanics of hearts with different degrees and combinations of electromechanical (ie, LBBB) and nonelectrical substrates of mechanical discoordination (ie, myocardial scar) were simulated. Based on these simulations, radial strain characteristics for the different LV mechanical discoordination substrates were obtained. By applying custom-made software, the systolic stretch index (as the sum of the posterolateral systolic prestretch and the septal systolic rebound stretch) was automatically calculated. The acute effects of CRT were evaluated in the different simulations, enabling predicting the hemodynamic response. In electromechanical LBBB-like substrate, the pattern of LV contraction was characterized by early septal contraction and posterolateral systolic prestretch occurring before aortic valve opening and late posterolateral contraction associated with septal systolic rebound stretch occurring during or after aortic valve closure. The amplitude of the contraction was more pronounced with increasing LBBB activation delay, resulting in larger systolic stretch index. In contrast, in nonelectrical substrates, the relatively strong contraction of the septal myocardium was accompanied by thinning of the weakened posterolateral myocardium during the isovolumic contraction phase and did not reverse at the end of the ejection phase, resulting in smaller systolic stretch index. Interestingly, the peak-to-peak radial strain delay increased along with the LBBB activation delay, with increasing local stiffness (more scar) and with decreasing local contractility. The response to CRT differed significantly across the different substrates: although in LBBB-like substrate, CRT increased cardiac output when the mechanical delay exceeded 60 ms, nonelectrical substrates did not show response to CRT independently of the magnitude of the peak-to-peak radial strain delay. These findings were corroborated in a group of 191 heart failure patients for whom the systolic stretch index was calculated from radial strain speckle tracking echocardiography. The value of systolic stretch index to predict response and its prognostic implications was assessed. Patients showing a systolic stretch index cut-off value of ≥9.7%, the most representative for favorable CRT response, were more frequently women, had less frequently ischemic heart disease, and showed more frequently LBBB QRS configuration and longer QRS duration than their counterparts. Interestingly, a systolic stretch index ≥9.7% was independently associated with better survival and freedom from heart failure hospitalization, heart transplant, or LV-assist device implantation after adjusting for QRS morphology and duration. These findings were also reproduced in the subgroup of patients with QRS durations between 120 and 149 ms or with non-LBBB morphology, although this subgroup of patients was relatively small.

In contrast to electrocardiography imaging (electrophysiological model), this electroanatomical model proposed by Lumens et al has the advantage of using echocardiography, a more widely used imaging technique in clinical practice than computed tomography and without the potential harmful effects of radiation exposure. In addition, the present model takes into consideration the mechanics of the myocardium, which have demonstrated a large impact on the response to CRT. Prospective studies comparing both modalities to select patients for CRT may help to understand which cardiac modeling may be more useful to predict the outcome of CRT. In addition, this comparison may establish whether ventricular electric uncoupling or systolic stretch index would be the LV dyssynchrony parameter yielding the optimal sensitivity and specificity to predict response to CRT. Meanwhile, ongoing work will elucidate how much patient-specific data are needed to generate cardiac models with adequate predictive value to guide individual patient treatment.

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References


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