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Phase II trials in heart failure: The role of cardiovascular imaging

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Abstract

The development of new therapies for heart failure (HF), especially acute HF, has proven to be quite challenging; and therapies evaluated in HF have greatly outnumbered treatments that are eventually successful in obtaining regulatory approval. Thus, the development of therapies for HF remains a vexing problem for pharmaceutical and device companies, clinical trialists, and health care professionals. Nowhere is this more apparent than in the phase II HF clinical trial, in which the goal is to determine whether an investigational agent should move forward to a phase III trial. Recent advancements in noninvasive cardiovascular imaging have allowed a new era of comprehensive phenotyping of cardiac structure and function in phase II HF trials. Besides using imaging parameters to predict success of subsequent phase III outcome studies, it is essential to also use imaging in phase II HF trials in a way that increases understanding of drug or device mechanism. Determination of the patients who would benefit most from a particular drug or device could decrease heterogeneity of phase III trial participants and lead to more successful HF clinical trials. In this review, we outline advantages and disadvantages of imaging various aspects of cardiac structure and function that are potential targets for therapy in HF, compare and contrast imaging modalities, provide practical advice for the use of cardiovascular imaging in drug development, and conclude with some novel uses of cardiac imaging in phase II HF trials.

The development of new therapies for heart failure (HF) has proven to be quite challenging. With the aging of the population and improvements in treatment of coronary artery disease,

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rates of HF are rising, making HF the most common cause of hospitalization in those age >65 years.¹ Thus, the market for a new drug or therapy for HF is large; and the potential benefit to both the individual patient and society as a whole is great. However, therapies evaluated in HF (especially acute HF) have greatly outnumbered treatments that are ultimately successful in obtaining Food and Drug Administration approval²; and even when treatments of HF are Food and Drug Administration approved, they are sometimes plagued by postmarketing studies that suggest worsened clinical outcomes.³ Therefore, the development of therapies for HF remains a vexing problem for pharmaceutical and device companies, clinical trialists, and health care professionals. In this review, we aim to (1) highlight the importance of cardiovascular imaging for HF trials with a focus on phase II studies; (2) outline various aspects of cardiac structure and function that are potential targets for therapy in HF, with possibilities, advantages, and disadvantages of various imaging modalities for each target; and (3) discuss potential novel uses of imaging techniques in phase II HF trials.

What is missing in phase II HF trials?

At the crux of the problem of developing new therapies for HF are phase II clinical trials. Although the phases of drug development (phases I-IV) are well known, in reality, the boundaries between the various phases are often blurred, especially when it comes to HF.⁴⁻⁶ Although phase II trials often evaluate the effectiveness and safety of varying doses of drugs in a limited number of patients, these trials vary considerably on type of clinical end point, even within HF (online Appendix A). Some phase II trials focus on safety and pharmacokinetics within a group of patients with HF, thus resembling a phase I study. More commonly, phase II trials include clinical end points along with surrogate end points, thus resembling a phase III study. The desire to include hard clinical end points (such as length of stay, hospitalization, and death) in phase II trials of HF stems from the disappointing translation of improvements in surrogate end points, such as hemodynamics, to improvements in clinical outcomes.^{2,4} Many drugs have lowered pulmonary capillary wedge pressure or increased cardiac output in phase II studies, only to have no effect on (or even increase) morbidity and mortality in large phase III studies.⁷⁻⁹ Compounding the problems associated with these hemodynamic phase II studies is the invasive nature of the typical pulmonary artery catheter monitoring, which can be harmful to patients and which preclude long-term acquisition of data.

In a time where increasingly more therapies for HF are focusing on long-term improvement in outcomes, the need to stretch beyond simple, short-term hemodynamic measurements (and possibly other surrogate end points) is more critical than ever. Fortunately, noninvasive cardiovascular imaging has advanced considerably,^{10,11} thereby allowing a new era for phase II trials in HF. Although these new imaging-based intermediate end points may or may not eventually translate into clinical outcomes, they have the unique ability to augment our understanding of the mechanisms underlying potential therapeutic benefit. Imaging may also be able to reduce heterogeneity when it comes to patient selection, which may translate into better clinical trial outcomes. A more comprehensive view of cardiovascular function, beyond traditional hemodynamics (using the imaging techniques outlined below), is, therefore, sorely needed to augment the phase II HF trial.

Hemodynamics

Hemodynamic parameters, particularly filling pressures and cardiac output, have been the time-honored, traditional surrogate end points in phase II trials of HF. Unfortunately, as outlined above, improvements in hemodynamics have not translated into improvements in hard clinical end points in phase III trials of HF and provide only limited mechanistic insight

into a particular drug or device. Thus, it is imperative that investigators involved in phase II trials of HF go beyond simple hemodynamics to avoid getting “lost in translation.” In addition to poor translation to improvement in clinical outcomes and patient discomfort, hemodynamic end points typically require continuous monitoring, which can result in increased costs. For phase II clinical trials of new therapies for HF, noninvasive imaging can be used to gather hemodynamic data when required. Doppler and tissue Doppler echocardiography, in particular, can provide a complete noninvasive assessment of cardiac hemodynamics, as described in detail previously¹² (see also online Appendix B).

Currently, Doppler echocardiography is the best suited imaging modality for noninvasive quantification of hemodynamic parameters because of its ability to capture data at high frame rates. However, although noninvasive hemodynamic assessment with Doppler echocardiography is performed routinely in patients with HF, the appropriateness of these methods is somewhat controversial. For example, the ability to accurately quantify left ventricular (LV) filling pressure noninvasively has recently been challenged.^{13,14} For this reason, phase II HF trials that are smaller in size or are more focused on drug mechanism may benefit from a simultaneous invasive (eg, pulmonary artery catheter) and noninvasive (eg, echocardiography) techniques for pressure-volume analysis, which can add sophistication to hemodynamic assessment in the trial.

Cardiac structure/remodeling

The thorough evaluation of cardiac structure and remodeling in phase II HF trials may provide insight into potential long-term clinical benefits of the study drug. In chronic HF, reductions in LV end-systolic and end-diastolic volumes may reflect beneficial reverse remodeling.¹⁵ In the acute setting, reductions in LV end-diastolic volume reflect decreased preload, whereas reductions in end-systolic volume reflect increased contractility. A decrease in left atrial volumes may reflect decreases in LV filling pressures over time, and parameters such as left atrial ejection fraction (EF) may be calculated to understand the effect of an investigational agent on left atrial mechanics.¹⁶⁻¹⁹ Right ventricular (RV) structure can also be quantified by measurements such as RV dimensions and area (in the apical 4-chamber view on echocardiography) and RV volumes on cardiac magnetic resonance (CMR).^{20,21} Left ventricular and RV wall thickness and mass can also be determined using a variety of imaging techniques, including echocardiography and CMR. Although these parameters are best suited for chronic HF trials, the long-term effects of acute intervention in HF may be determined by long-term changes in LV and RV wall thickness or mass. Cardiac magnetic resonance is especially useful for detecting small differences in cardiac structure over time given its high spatial resolution, high reproducibility, and decreased variability, all of which can help reduce the sample size necessary for a particular trial.²² Nevertheless, like all imaging modalities, there are limitations to CMR such as increased variability depending on analyst experience and differing results based on technique used for determining boundaries of the LV.²³ Table I lists the advantages and disadvantages of various imaging modalities for the assessment of cardiac structural and remodeling phenotypes.

Left ventricular systolic function

Left ventricular systolic function can be evaluated using a wide variety of techniques in patients with HF. Ejection fraction has been the parameter used most widely in clinical HF trials but is load dependent. When used as an end point in phase II HF trials, echocardiographic LV volumes and EF should be measured using a biplane, volumetric technique instead of one that relies on LV dimensions. This method is recommended clinically by the American Society of Echocardiography,¹⁰ and it is easy to use in the HF

setting. In some phase II HF trials, it will be critical to evaluate for more subtle changes in LV volumes and EF. In these cases, using a 3-dimensional (3D) technique (such as 3D echocardiography or CMR) offers improved accuracy over 2-dimensional (2D) methods.^{24,25}

Although EF has been used in multiple clinical trials to date, it is now possible to noninvasively evaluate regional myocardial systolic function, with the ability to examine longitudinal, radial, and circumferential fiber shortening.^{26,27} For phase II HF trials, it is important to evaluate these subtle changes in systolic function in a quantitative, reliable, and reproducible manner. Imaging methods available for evaluating regional systolic function include tissue Doppler imaging (via pulsed or color tissue Doppler) and tissue tracking imaging (available in both echocardiography and CMR).²⁷⁻²⁹ Tissue Doppler imaging using pulsed Doppler has the advantage of ease of acquisition, faster interpretation by a core laboratory, and higher frame rate. However, pulsed Doppler only provides a “snapshot” of a single region of interest in the myocardium. Therefore, it is up to the sonographer to choose the correct region of the myocardium to analyze. Alternatively, color tissue Doppler allows for postprocessing of images, which allows the echocardiography core laboratory the freedom to choose the region of interest post hoc, thereby potentially improving the reliability of tissue Doppler velocity, strain, and strain rate measurements (Figure 1).

Tissue tracking is a novel technique that uses computerized algorithms to track pixels of imaging data (whether obtained by echocardiography or CMR^{27,30-33}) to quantify displacement, velocity, and strain of the myocardial region of interest. The advantage of tissue tracking is the lack of angle dependence. All Doppler imaging techniques suffer from the requirement that the movement of interest (eg, longitudinal motion of the lateral mitral annulus) must be aligned with the Doppler beam. Because of this limitation, Doppler imaging often underestimates velocities because of lack of optimal alignment; and only myocardial segments that are well aligned with the Doppler beam can be reliably analyzed. Tissue tracking, on the other hand, does not suffer from the angle dependence of tissue Doppler imaging and is, therefore, a powerful technique for the determination of regional myocardial velocities, strain, and torsion (Figure 2). The main disadvantage of tissue tracking using both echocardiography and CMR is lower frame rate compared with Doppler. Echocardiographic tissue tracking (which tracks ultrasound “speckles” in a region of interest over time) additionally requires high-quality images and may be suboptimal in 2D because these speckles go in and out of the imaging plane. Three-dimensional tissue tracking echocardiography has the potential to overcome these issues and is currently in development.^{34,35} Cardiac magnetic resonance also overcomes these issues because of its inherent 3D imaging capability.³²

Although potentially beneficial as surrogate end points in phase II HF trials, EF, tissue velocities, and strain all suffer from load dependence. Therefore, especially in patients with HF, it can be difficult to determine whether changes in these parameters are due to changes in intrinsic myocardial contractile properties or simply the change in preload and/or afterload. Pressure-volume analysis³⁶ is one way to overcome this limitation; however, most pressure-volume analysis methods require (at the very least) continuous invasive pressure measurements. Noninvasive pressure-volume analysis does exist (online Appendix C), but it remains to be seen whether these indices can help inform the mechanism of action or potential benefit of new therapies being tested in phase II HF trials. Table II lists the advantages and disadvantages of various indices of LV systolic function, along with recommended imaging modalities for each index.

Left ventricular diastolic function

Left ventricular diastolic dysfunction is increasingly being identified as a powerful predictor of poor outcome in a wide variety of cardiovascular disease states, including HF.³⁸⁻⁴⁰ In acute HF, changes in diastolic function most likely reflect acute changes in preload. For example, in the patient with HF, the rapid transition from grade III (severe) diastolic dysfunction to grade I (mild diastolic dysfunction) on echocardiography indicates that LV filling pressure has decreased rapidly as a response to therapy. This can be an important noninvasive end point in HF trials but does not imply that intrinsic diastolic stiffness of the myocardium has changed acutely given the load dependence of diastolic parameters such as transmitral flow (including E velocity, E/A ratio, deceleration time, and isovolumic relaxation time) and pulmonary vein flow. Tissue Doppler imaging (along with tissue tracking imaging) can evaluate diastolic stiffness of the myocardium and may be able to signal acute improvements in diastolic compliance in the HF setting.^{41,42} However, even early diastolic tissue velocities (eg, E') can be load dependent.⁴³ Therefore, it is critically important to show that improvements in E' with a study drug or device are independent of changes in preload or afterload.

Left ventricular diastolic chamber compliance can be estimated using a wide variety of techniques including evaluation of the early mitral inflow (E wave) deceleration time (a shorter deceleration time implies increased LV diastolic stiffness); the ratio of end-diastolic pressure (estimated by E/E' ratio) to end-diastolic volume; the ratio of E/E' to stroke volume;⁴⁴ and using a single-beat method, which relies upon the noninvasive determination of the LV end-diastolic pressure and LV end-diastolic volume.⁴⁵ All of the aforementioned techniques suffer from potential limitations in phase II trials of HF (see online Appendix D) and, therefore, require further examination within the phase II HF trial setting to determine use. Future phase II HF clinical trials of investigational agents thought to increase lusitropy may benefit from exploring these parameters in the invasive and noninvasive settings to determine whether noninvasive parameters can truly supplant invasive ones in the phase II setting. Table III lists the advantages and disadvantages of various indices for the assessment of LV diastolic function.

Right ventricular systolic and diastolic function

Right ventricular enlargement and RV systolic and diastolic dysfunction are important predictors of outcome in HF and represent a novel end point in phase II HF trials.^{20,46-50} The challenge in cardiovascular imaging (especially echocardiography) is the difficulty in standardized imaging and functional assessment of the RV. The RV is crescent shaped, making it difficult to quantify its size and systolic function. Three-dimensional echocardiography and CMR can overcome these limitations and allow for more accurate assessment of RV EF. When 3D echocardiography and CMR are not feasible, 2D and Doppler echocardiographic measurements such as tricuspid annular plane systolic excursion, myocardial performance index (Tei index), and tissue Doppler imaging of the RV free wall can also provide insight into RV function; and all 3 parameters can be measured in a reliable and reproducible fashion.²⁰ Regional RV function, using tissue tracking techniques, may provide additional mechanistic insight into the effects of new therapies for HF.

Coronary perfusion/myocardial viability

In phase II trials of HF, assessment of coronary perfusion and myocardial viability can be extremely important in helping to determine eligibility for the trial, provide mechanistic insights, and determine whether a particular drug or device is beneficial. For example, the presence or absence of viability or scar (in either ischemic or nonischemic cardiomyopathy) may help investigators understand whether there is a particular patient who has any hope for

myocardial recovery and may help select patients who will have the highest likelihood of benefiting from a new therapy and, therefore, should be included in the phase II trial.

Various imaging modalities are available for assessment of coronary perfusion and viability, including stress echocardiography, single photon emission computed tomographic (SPECT) imaging, CMR, and positron emission tomography (PET). Combined modality imaging such as cardiac computed tomography (for noninvasive coronary angiography) with PET imaging (for perfusion) can also be used for assessment of perfusion and viability. When imaging of coronary perfusion or viability is a key outcome of the trial (either for mechanistic insight into the study drug or device or as an end point of the trial), more quantitative analysis of perfusion and viability must be performed. In the case of coronary perfusion, adenosine SPECT, PET, and CMR all have the advantage of being able to quantify the amount of perfusion so that detection of changes between baseline and postrandomization can be detected. High-spatial resolution myocardial perfusion with CMR is a newer modality, which is highly accurate for the detection of coronary artery disease, and may allow the assessment of RV perfusion.⁵¹ Cardiac magnetic resonance-based assessment of perfusion has been studied in a multicenter, multivendor trial⁵² and has been found to be superior to SPECT imaging, which may make it the modality of choice for quantitative noninvasive assessment of coronary perfusion in phase II HF trials. In the case of viability, CMR is the current reference standard for quantitative assessment nonviable myocardium. Delayed enhancement contrast CMR can identify nonviable myocardium with excellent spatial resolution, and the transmural extent of contrast enhancement can be used as a guide for potential recovery of a particular myocardial segment⁵³ in both ischemic and nonischemic cardiomyopathies (Figure 3).

Novel uses of cardiovascular imaging in phase II HF trials

Two potentially novel uses of advanced cardiovascular imaging in phase II HF trials involve the ability of new imaging modalities to go beyond hemodynamic and structural phenotyping: (1) the ability to provide novel mechanistic insights and (2) the ability to further characterize and classify patients with HF in new ways. The advent of modalities such as CMR-based diffuse fibrosis imaging,⁵⁴ metabolism imaging using PET and magnetic resonance spectroscopy,^{55,56} and molecular imaging^{57,58} may allow us to further understand the mechanisms by which novel investigational drugs and devices provide benefit. By providing mechanistic insights in phase II trials of HF, imaging techniques may further inform all phases of drug or device development. For example, important mechanistic insights could provide the rationale to reexamine preclinical models, develop new uses for investigational agents, and ultimately help determine which patients may benefit most in phase III trials.

The use of novel imaging techniques and modalities may also provide assistance in our elusive ability to further categorize patients with HF. Heart failure, a heterogeneous syndrome, has benefited, thus, far from a “one-size-fits-all” approach to therapy, especially in those patients with HF and reduced EF. Thus, drugs such as β -blockers and renin-angiotensin-aldosterone inhibitors and devices such as cardiac resynchronization therapy have improved outcomes in a wide variety of patients. The result, however, is a newfound difficulty in finding drugs and devices that provide additional benefit in HF above and beyond currently approved evidence-based therapies. In the future, advanced cardiovascular imaging techniques may be able to accurately categorize patients for targeted intervention, thereby increasing the likelihood of success for a novel therapeutic agent. For example, CMR diffuse fibrosis imaging may be able to select patients most likely to benefit from an antifibrotic therapy.

Practical considerations for the use of cardiovascular imaging in phase II HF trials

The importance of a core laboratory for centralized interpretation of cardiovascular tests for clinical trials in cardiovascular disease is well established, and their use in phase II HF trials cannot be underestimated. An excellent consensus statement for the conduct of echocardiographic imaging in clinical trials was recently published,⁵⁹ and many of the principles outlined apply to other imaging modalities as well (see online Appendix E). Thus far, echocardiography has been used most commonly both as screening for entry and for assessment of outcome; but the use of additional imaging modalities (especially CMR) continues to expand. Several prior phase II HF studies have used imaging end points with varying degrees of success, and study of these prior trials can provide valuable lessons on the conduct of imaging in phase II HF studies (see online Appendix F).

In the future, besides using imaging solely for screening or end points in clinical trials, phase II HF trials will benefit greatly by using imaging for (1) better understanding mechanisms of therapeutic benefit and (2) reducing patient heterogeneity in subsequent phase III trials, both of which are especially important given the critical need for improved categorization of the HF syndrome.⁶⁰ Figure 4 illustrates the potential use of cardiovascular imaging for 2 different hypothetical drugs in development for HF, highlighting the principles of enhancing mechanistic insight and improving patient selection.

Limitations of cardiovascular imaging techniques in phase II HF trials

The ability to use cardiovascular imaging techniques in HF trials relies heavily on the quality images, quality of core laboratory interpretation, and reliability of measurements made. Several techniques to improve imaging and decrease variability in measurements in imaging studies have been published,^{10,23,59} and these suggestions should be implemented in the planning stages of future phase II HF trials. Nevertheless, unlike invasive hemodynamics, signal quality can be quite variable from patient to patient, even when image optimization techniques are used.

The Achilles heel of phase II trials in HF has been the failure of improvements in traditional hemodynamic end points (and other intermediate end points such as exercise capacity, short-term symptom improvement, and even echocardiographic measurements) to translate into benefits in hard clinical end points in phase III trials.^{2,4} Cardiovascular imaging end points may suffer from the same fate and, therefore, must be tested adequately in phase II trials to determine whether they will translate into true improvements in phase III trials.

Measurement of cardiovascular imaging parameters at multiple time points instead of a single time point in the phase II trial may allow for better identification of HF therapies that are truly beneficial. Instead of simply looking for cardiovascular imaging to be a new marker of benefit, serial changes in cardiac structure and function may assist in our understanding of how a new HF therapy may benefit patients. In addition, cardiovascular imaging's primary role in future phase II HF trials may be its critical use in patient selection for targeted therapies and for mechanistic insights into novel drugs or devices. Regardless of the use of imaging in phase II HF trials, it should be stressed that imaging alone should not be the only end points. Other markers of efficacy, including biomarkers, exercise capacity, and quality of life scores will add validity to the imaging findings and may provide additional mechanistic insights for a particular drug or device. Despite these limitations, for other cardiovascular diseases (eg, atherosclerosis), studying the effects of new therapies on imaging parameters (eg, intravascular ultrasound) has proven quite useful.⁶² Indeed, the use of intravascular ultrasound in atherosclerosis clinical trials serves as a model for the use of

imaging to better understand disease mechanism, progression, and relationship to clinical outcomes in phase II HF trials.

Conclusions

Important advances in cardiovascular imaging now allow for detailed characterization of a wide variety of cardiovascular structural and functional phenotypes in HF. Although phase II HF trials are beginning to successfully include advanced imaging techniques,^{63,64} there is still a large gap between advances in noninvasive imaging techniques and their use in clinical HF trials. Several imaging modalities exist, and those involved in HF clinical trials must understand the available imaging parameters (Tables I-III) and the advantages, disadvantages, and relative costs of each imaging modality (Table IV). By understanding the advantages and disadvantages of the various imaging modalities and the various structural/functional imaging targets, industry and investigators alike will be better equipped to conduct phase II trials in HF.

A new definition of the phase II HF trial, which emphasizes the mechanistic understanding of a new HF therapy rather than improvement in surrogate end points, should assist in the search for new HF therapies. In this respect, cardiovascular imaging techniques are poised to make a large impact in phase II trials of HF because they can go beyond other intermediate trial end points by providing mechanistic insights into investigational drugs and devices. In addition, one of the most exciting future uses of imaging in the phase II HF trials is for improved classification of underlying pathology and pathophysiology (with resultant decreased patient heterogeneity), which should help the conduct of trials of targeted HF therapy. The future of cardiovascular imaging in HF clinical trials is, therefore, bright; but progress in the use of new cardiovascular imaging techniques will depend on the implementation and thorough evaluation of these new modalities in phase II trials of HF.

Appendix A. Systematic review of cardiovascular imaging in phase II HF studies

To better determine the use of cardiovascular imaging in phase II heart failure (HF) studies, we systematically searched ClinicalTrials.gov⁶⁵ using the following strategy: Under the “Search for Clinical Trials” hyperlink, we selected the “Advanced Search” tab and used the following search criteria: search term, “heart failure”; study type, “interventional studies”; phase, “Phase II.” Our search resulted in 487 studies; and the conditions, interventions, and outcomes for each study were reviewed. Of the 487 studies, 237 were specifically aimed at patients with HF (the other studies simply contained the key words “heart failure”; eg, HF was one of the outcomes; but the study was a chemotherapy study).

Review of these 237 HF studies reveals that although all were categorized by sponsors and investigators as “phase II,” there was considerable heterogeneity in trial end points, ranging from pharmacokinetic studies to hard clinical outcomes and a variety of measures in between (including symptom questionnaires, bio-markers, exercise capacity, and imaging). Figure A1 displays the frequency of cardiovascular imaging in these 237 primary HF studies and shows that use of imaging has become more frequent in phase II HF studies over time (52% of open studies compared with 26% of closed studies contain imaging end points). The use of cardiac magnetic resonance (CMR) has also increased (20% of open studies compared with 8% of closed studies). Most studies aimed to use cardiovascular imaging as an end point for left ventricular (LV) structure (remodeling) and ejection fraction. Relatively few studies included measurements of LV diastolic function, tissue Doppler imaging, strain, metabolic imaging, viability, perfusion, or delayed enhancement. Thus, although the use of

cardiovascular imaging in phase II HF trials is increasing, there is still a paucity of advanced imaging techniques in these trials.

Appendix B. Noninvasive evaluation of cardiac hemodynamics

For phase II clinical trials of new therapies for HF, noninvasive imaging can be used to gather hemodynamic data when required. Doppler and tissue Doppler echocardiography, in particular, can provide information on right atrial pressure (through visualization of the vena cava during respiration,⁶⁶ analysis of hepatic vein flow,⁶⁷ or Doppler and tissue Doppler imaging of the tricuspid valve⁶⁸); pulmonary artery systolic pressure (based on the tricuspid regurgitant peak velocity⁶⁹); pulmonary artery diastolic pressure (based on the pulmonic regurgitation enddiastolic velocity)⁷⁰; LV filling pressures (based on the ratio of early mitral inflow to early mitral annular diastolic velocity $[E/E']$)^{71,72}; and cardiac output (based on Doppler evaluation of the LV outflow). Even pulmonary vascular resistance and systemic vascular resistance can be calculated noninvasively.^{73,74} Use of noninvasive echocardiographic estimates of cardiac hemodynamics has recently been validated in patients with acute decompensated HF.⁷⁵

Appendix C. LV systolic function: noninvasive pressure-volume analysis

Examples of noninvasive pressure-volume analysis include end-systolic elastance (the slope of the end-systolic pressure-volume relationship),⁷⁶ preload recruitable stroke work,⁷⁷ and the stroke work/end-diastolic volume ratio. End-systolic elastance, a relatively load-independent measure of LV contractility, can be estimated in a crude fashion as the ratio of end-systolic pressure to end-systolic volume.^{78,79} End-systolic pressure can be estimated as $0.9 \times$ systolic blood pressure or can alternatively be estimated by obtaining estimated central aortic pressure waveforms using arterial tonometry.⁸⁰ Another way to estimate end-systolic elastance involves using a single-beat method, which incorporates noninvasive blood pressure along with echocardiography-derived LV volumes, stroke volume, and systolic time intervals.⁷⁶

Appendix D. LV diastolic function: limitations of LV compliance parameters

All noninvasive imaging-based techniques to determine LV diastolic compliance suffer from potential limitations in phase II trials of HF. Deceleration time may change significantly with changes in preload and minor changes in deceleration time may be difficult to detect in the acute setting. The ratio of estimated end-diastolic pressure to end-diastolic volume is a very rough estimate of the curvilinear end-diastolic pressure-volume relationship (EDPVR). For this reason, some investigators have used the ratio of noninvasive end-diastolic pressure/stroke volume as a better way to estimate the true shape of the EDPVR curve. However, this parameter cannot be used reliably in most HF trials because any investigational agent, which increases stroke volume (eg, positive inotrope), will also lower the $E/E'/$ stroke volume ratio independent of any true effect on the EDPVR. In addition, in the acute setting, it may be difficult to detect changes in LV diastolic chamber compliance with the single-beat method for characterization of the curvilinear EDPVR because it is unlikely that a therapy will improve LV chamber compliance acutely, especially in patients with HF.

Appendix E. Practical considerations for the imaging core laboratory

The importance of a core laboratory for centralized interpretation of cardiovascular tests for clinical trials in cardiovascular disease is well established.⁸¹ Several studies have found that local site interpretation of tests such as electrocardiography and echocardiography is inferior to core laboratory interpretation and can lead to deleterious clinical consequences in some

instances.⁸¹⁻⁸⁴ Therefore, it is essential that an imaging core laboratory be part of phase II trials of HF.

Cardiovascular imaging interpretation by core laboratories has been successful in several chronic HF trials, most of which have used echocardiography in phase III clinical trials. Examples include SAVE, SOLVD, V-HeFT I/II, MIRACLE, and CHARM.⁸⁵⁻⁸⁹ In each of these large trials, an echocardiography core laboratory was used; and examples of measurements made were LV dimensions, volumes, ejection fraction, and/or mass, along with grading of mitral regurgitation. In most of these and other HF trials, echocardiography has been used as screening for entry and for assessment of outcome; and the core laboratory plays a key role in performing these functions.⁸¹ There has also been increasing use of CMR core laboratories for screening (eg, presence of delayed enhancement⁹⁰) and outcome (eg, LV end-systolic volume⁹¹) in trials of patients with LV dysfunction and HF, which supports the feasibility of CMR in the clinical trial setting. Regardless of the imaging modality, one of the key advantages of phase II HF trials is the smaller number of subjects (compared with phase III trials with hard clinical end points), thereby allowing the imaging core laboratory and clinical trialists to work together closely for improved training and feedback for study sites and more detailed phenotyping of cardiac structure and function.

The American Society of Echocardiography has published guidelines on the use of echocardiography in clinical trials,^{59,81} and many of the suggestions made for echocardiography apply to all cardiovascular imaging modalities used in phase II HF trials. Some of the key points for creation of a core laboratory and imaging protocol for phase II HF trials include the following. A principal investigator (PI) of the imaging core laboratory should be named and should have the technical expertise and experience in both the conduct of clinical trials and in the chosen imaging modality. Importantly, centralized or on-site training of imaging technicians and investigators is essential. One of the problems frequently encountered in phase II trials in HF is that, in most cases, the site PI does not have expertise and is often not involved in the cardiovascular imaging aspects of the trial. Because local cardiovascular imaging specialists at the trial site are not invested in the clinical trial, the quality assurance of the imaging technique may be lacking. In large clinical trials, imaging site PIs can be identified; but this is often not practical in smaller phase II trials in HF. Therefore, it is vitally important to adequately train and educate both the local site PI as well as the imaging technician(s) who will be working on the phase II clinical trial. When on-site or centralized training is not feasible, the use of videoconferencing and/or online instructional videos is essential.

Part of the instructional content in phase II trials of HF should include detailed and thorough operations manual describing the trial's imaging protocol. Beyond step-by-step instructions of the imaging protocol, the manual should also include the specific imaging end points to be measured by the core laboratory, the rationale for those end points, and a description of how measurements will be made by the core laboratory to define those end points. For example, if LV diastolic function is an end point in the trial, there should be a detailed a priori description of how LV diastolic function will be analyzed and graded.

Other practical considerations include the ability of the core laboratory to receive imaging studies through a secure file transfer protocol connection (especially important for HF trials which may need immediate interpretation of images to determine eligibility for the clinical trial); use of the same imaging machine and same sonographer for all patients recruited at an individual site (if possible); and site approval by the imaging core laboratory (after sample imaging studies have been examined by the core laboratory) before the recruitment of study patients.

Appendix F. Examples of the use of cardiovascular imaging in phase II HF trials

As shown in the aforementioned analysis of www.ClinicalTrials.gov data, there are several phase II HF studies that have used or are using cardiovascular imaging end points; and this number continues to grow. Examples of prior phase II HF trials, which have demonstrated utility of imaging end points include MOCHA,⁹² EARTH,⁹¹ and HORIZON-HF.^{63,64}

- MOCHA trial⁹² was a phase II randomized trial of carvedilol versus placebo in 345 patients with chronic HF with reduced LV ejection fraction ($< 35\%$). Using radionuclide ventriculography, the MOCHA investigators found that there was a dose-dependent increase in LV ejection fraction with carvedilol compared with placebo, a change that was concordant with improvements in all-cause mortality and HF hospitalization.
- EARTH⁹¹ was a phase II randomized trial of darusentan versus placebo in 642 patients with chronic systolic HF in which change in LV end-systolic volume (measured by cardiac magnetic resonance imaging) was the primary end point. The EARTH investigators specifically sought to determine whether darusentan improved LV remodeling to determine whether to move forward to a phase III outcomes trial. The EARTH trial showed that, at 6 months, there was no difference in the primary outcome of change in LV end-systolic volume in the darusentan and placebo groups. Based on these results, the authors concluded that it would be unlikely for darusentan to improve mortality in chronic HF. Indeed, subsequent trials using endothelin receptor blockers for HF have failed to show improved clinical outcomes.
- In HORIZON-HF trial,^{63,64} 120 patients with acute HF syndromes and reduced LV ejection fraction were randomized 3:1 (3 dose groups of istaroxime vs placebo). In this study, the investigators investigated changes in LV volume and systolic function (ejection fraction) but also used Doppler and tissue Doppler imaging to evaluate LV diastolic function. In addition to reducing LV volumes and increasing contractility, istaroxime administration resulted in improved diastolic function, which corresponded to reductions in pulmonary capillary wedge pressure. Whether these changes are associated with improvements in eventual clinical outcome will be tested in future studies.

Figure A1

Use of cardiovascular imaging in closed and open phase II HF studies listed on www.clinicaltrials.gov. *Some trials contained >1 imaging outcome. *CV*, Cardiovascular; *MR*, magnetic resonance; *SPECT*, single photon emission computed tomography; *PET*, positron emission tomography; *CT*, computed tomography; *ERNA*, equilibrium radionuclide angiography.

It should be noted that there are also examples of clinical trials of HF, which show lack of improvement in cardiac remodeling but still demonstrate improved outcomes. Eplerenone, an aldosterone antagonist, has recently been found to reduced death and hospitalization in patients with mild chronic HF with reduced LV ejection fraction.⁹³ However, in a similar patient population, eplerenone was not associated with reduction in either LV end-diastolic or end-systolic volumes by radionuclide ventriculography.⁹⁴ Although the latter imaging study was considerably smaller than the outcomes study and possibly limited by imaging technique, the study design should have been sufficient to detect clinically significant improvements in LV remodeling.

These results demonstrate that cardiovascular imaging intermediate end points are not failsafe; the lack of improvement in imaging end points does not necessarily imply inability to detect improvements in outcomes, thus underscoring the need to use more than imaging to determine whether a particular drug or device should advance from a phase II to phase III clinical trial. Furthermore, these results support the additional use of cardiovascular imaging (beyond an intermediate or surrogate end point) as a tool to perform detailed mechanistic studies in phase II HF trials to obtain the full benefit of the imaging techniques and to decrease heterogeneity in HF trials.

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Figure 1.

Comparison of pulsed tissue Doppler, color tissue Doppler, and tissue tracking imaging for determination of longitudinal tissue velocities. In this sample patient with HF and preserved EF, pulsed tissue Doppler imaging (top panel) allows for a single snapshot of longitudinal lateral mitral annular tissue velocities, controlled by the local site sonographer. In the pulsed tissue Doppler image (top panel), note the poor placement of the sample volume (on the atrial side of the mitral annulus) and suboptimal velocity scale. Color tissue Doppler and tissue tracking imaging (middle and bottom panels, respectively) both allow for post hoc sample volume placement and analysis by the core laboratory, which allows for improved quality control.

Figure 2.

Tissue tracking echocardiographic assessment of LV torsion. Tissue tracking echocardiography can be used to determine the presence of normal or abnormal LV torsion. Normally, the apex (left panel) contracts in a counter-clockwise fashion, whereas the base (right panel) contracts in a clockwise fashion. The graphs below the images show the rotation (in degrees) of the epicardium (blue), midmyocardium (yellow), and endocardium (red). Positive numbers denote counterclockwise rotation, and negative numbers denote clockwise rotation (in degrees).

Figure 3.

Comparison of myocardial scar patterns on CMR imaging. Location and distribution of delayed contrast enhancement (scar; see arrows) on CMR imaging can help understand underlying myocardial pathology as shown in 3 patients, all of whom have HF with reduced EF. Scar can be localized to the subendocardium (top panel, inferior and inferolateral walls) in patients who have had a nontransmural myocardial infarction; scar can be transmural (middle panel, anteroseptal, anterior, apical, and anterolateral walls) in patients who have suffered from transmural myocardial infarction; and scar can be diffuse and located in the midmyocardium (bottom panel) in patients with nonischemic cardiomyopathy. Differences in scar location, extent, and burden in patients with HF may be useful enrollment criteria for future phase II trials of targeted therapies.

Figure 4.

Hypothetical examples of cardiovascular imaging in the HF drug development process. *See Gheorghiade et al⁶¹ for detailed description of T1 phase of drug development. **A**, Hypothetical scenario for a drug in development for HF and reduced EF (systolic HF). **B**, Hypothetical scenario for a drug in development for HF with preserved EF (diastolic HF).

Table I
Comparison of imaging modalities for cardiac structure/remodeling

Imaging Technique	Advantages	Disadvantages	Variability	Ease of use
Linear measurements				
M-mode echocardiography	Reproducible; large body of experience; high frame rate	Single-dimension not representative in distorted ventricles; beam orientation may be off-axis [*] , leading to overestimation of dimensions and wall thickness; decreased accuracy in presence of wall motion abnormalities; errors magnified when formulas used (eg, cubic formula for LV mass)	+	++++
2D guided	Ensures proper alignment of acquisition, perpendicular to the long axis of the LV	Single-dimension not representative in distorted ventricles; lower frame rate than M-mode; decreased accuracy in presence of wall motion abnormalities; errors magnified when formulas used (eg, cubic formula for LV mass)	++	++++
2D-derived volumes, mass				
2D echocardiography	More representative in distorted ventricles (especially when using biplane method of discs for LV volumes and truncated ellipsoid method for LV mass)	Based on geometric assumptions	++	+++
3D-derived volumes, mass				
3D-echocardiography	True volumetric technique	Requires additional postprocessing time; depends on image quality; irregular rhythm and breathing artifacts can cause artifact [†]	++	++
CMR	True volumetric technique; criterion standard	Requires additional postprocessing time; arrhythmia can cause artifacts; more expensive	+	++

^{*} Anatomical M-mode is a new echocardiography technique that can allow for post hoc placement of M-mode beam so that it is perpendicular to the LV long axis; however, frame rate is lower than in traditional M-mode.

[†] Newer 3D echocardiography machines can acquire data in a single beat, thereby minimizing these disadvantages.

Table II

Comparison of indices of LV systolic function

Index	Advantages	Disadvantages	Load dependence	Variability	Ease of use
Ejection phase indices					
EF	Widespread use and familiarity	Changes with loading conditions, heart rate	+++	++	+++
Systolic time intervals	Requires very little imaging data	Changes with loading conditions, heart rate	+++	++	+++
Regional myocardial velocities, strain, strain rate	More sensitive to subtle changes than EF; allows evaluation of radial, circumferential, and longitudinal function	Changes with loading conditions	+++	++	+++
Isovolumic indices					
Isovolumic contraction time	Ease of use	Preload dependent	++	++	+++
dP/dt	Ease of use; largely independent of systemic arterial pressures; does not require geometric assumptions	Preload dependent; for noninvasive estimation, requires presence of mitral regurgitation	++	++	+++
Pressure-volume analysis					
Noninvasive single-beat method *	Relatively load independent	Not extensively validated in large, dilated hearts; requires multiple measurements; dependent heavily on systolic time intervals	+	++	+
End-systolic pressure/volume ratio	Relatively load independent; not based on mathematical assumptions	Assumes V_0 is equal to 0; may be less useful in large, dilated hearts	+	++	+++
End-systolic stress—velocity of circumferential fiber shortening relation	Relatively load independent	Based on mathematical assumptions and linear dimensions of LV	+	+++	+

* See reference by Chen et al.³⁷

Table III

Comparison of indices for LV diastolic function

Index	Advantages	Disadvantages	Load dependence	Variability	Ease of use
Doppler-derived indices					
E wave velocity, E/A ratio	Ease of use	Load dependent	++++	+	++++
E wave deceleration time	Ease of use	Load dependent; small changes in measurement are equal to large changes in deceleration time	++++	++	++++
Pulmonary venous flow characteristics	Allows noninvasive estimation of LV filling pressures	Difficult to obtain high-quality data in some patients	++++	++	+++
Color M-mode velocity of propagation	Allows noninvasive estimation of LV filling pressures	Accurate and reliable acquisition of data is difficult	++++	+++	++
Tissue Doppler indices					
E'	Ease of use; less load dependent than other echocardiographic indices of diastolic function	Angle dependency of Doppler and tissue Doppler	++	++	++++
E/E' ratio	Allows noninvasive estimation of LV filling pressures	Angle dependency of Doppler and tissue Doppler; large "gray zone," where LV filling pressures are indeterminate; may be less accurate in patients with EF <30%	++++	++	++++
Pressure-volume analysis					
Noninvasive single-beat method [*]	Constructs curvilinear end-diastolic pressure-volume curve	Requires noninvasive estimate of end-diastolic pressure	+	++	++
End-diastolic pressure/end-diastolic volume	Ease of use	Requires noninvasive estimate of end-diastolic pressure; may not accurately represent true curvilinear EDPVR	++	++	++++
End-diastolic pressure/stroke volume	Ease of use	Requires noninvasive estimate of end-diastolic pressure; will decrease with increasing contractility (which will decrease stroke volume)	++	++	++++

EDPVR, End-diastolic pressure-volume relationship.

^{*} See reference by Klotz et al.⁴⁵

Table IV
Overall comparison of imaging modalities

Imaging modality	Advantages	Disadvantages	Relative costcost
Echocardiography (including tissue Doppler, tissue tracking, and 3D imaging)	Portable, ease of obtaining images in sick patients No radiation Ability to quantify volumes, mass, valvular lesions, ischemia, strain, and viability Allows for noninvasive estimation of intracardiac pressures Repeated measurements possible in a 24- to 48-h period	Lack of reproducibility Image quality may be poor Unable to perform fibrosis or scar imaging at the present time	+ / ++
SPECT/PET/nuclear imaging	Allows for evaluation of ischemia, viability, metabolic imaging	Radiation Not portable in most cases	+++
Computed tomography	Allows for evaluation of cardiac structure and coronary anatomy	Radiation Not portable Patients with HF are at risk for contrast nephropathy	+++
Magnetic resonance imaging	Detailed evaluation of cardiac structure (volumes, mass, valvular lesions), scar, and fibrosis Ability to image for ischemia and viability Best reproducibility	Not portable Difficult for patients with acute HF Potentially dangerous in patients with low GFR (risk of nephrogenic fibrosing dermatopathy) Inability to image patients with current-generation devices (eg, pacemakers, ICDs)	++++

GFR, Glomerular filtration rate; *ICD*, implantable cardioverter defibrillator.