Development of Therapeutics for Heart Failure

Large Animal Models of Heart Failure
A Critical Link in the Translation of Basic Science to Clinical Practice

Jennifer A. Dixon, MD; Francis G. Spinale, MD, PhD

Abstract—Congestive heart failure (HF) is a clinical syndrome, with hallmarks of fatigue and dyspnea, that continues to be highly prevalent and morbid. Because of the growing burden of HF as the population ages, the need to develop new pharmacological treatments and therapeutic interventions is of paramount importance. Common pathophysiologic features of HF include changes in left ventricle structure, function, and neurohormonal activation. The recapitulation of the HF phenotype in large animal models can allow for the translation of basic science discoveries into clinical therapies. Models of myocardial infarction/ischemia, ischemic cardiomyopathy, ventricular pressure and volume overload, and pacing-induced dilated cardiomyopathy have been created in dogs, pigs, and sheep for the investigation of HF and potential therapies. Large animal models recapitulating the clinical HF phenotype and translating basic science to clinical applications have successfully traveled the journey from bench to bedside. Undoubtedly, large animal models of HF will continue to play a crucial role in the elucidation of biological pathways involved in HF and the development and refinement of HF therapies. (Circ Heart Fail. 2009;2:262-271.)

Key Words: myocardial infarction ■ myocardial remodeling ■ overload states ■ rapid pacing

Congestive heart failure (HF) is a constellation of symptoms, with hallmarks of fatigue and dyspnea, which continues to be a highly prevalent and morbid clinical syndrome. Although the etiologic underpinnings of HF can be diverse, common pathophysiologic features include changes in left ventricle (LV) structure, function, and neurohormonal activation. The impact of HF will undoubtedly become even more substantial as the population ages. Accordingly, the need to develop new pharmacological treatments and therapeutic interventions for HF is of paramount importance. The journey from discovery, to understanding, to clinical application of the biological basis of HF is one that can only be traveled with the use of large animal models that recapitulate this clinical phenotype.

The current pharmacological armamentarium in the treatment of HF includes angiotensin-converting enzyme inhibitors, aldosterone antagonists, and angiotensin and β-adrenergic receptor blockade.1 Although inhibition of the renin-angiotensin-aldosterone and sympathetic adrenergic systems have provided clear benefit to those suffering from HF, the disease process nonetheless continues. Therefore, further research is required to find additional pathways and mechanisms to target in the battle against HF.

The Need for Large Animal Models of HF
Significant insight into the molecular and cellular basis of cardiovascular biology has come from small animal models, particularly mice. However, significant differences exist with regard to cardiac characteristics such as heart rate, oxygen consumption, adrenergic receptor ratios, and response to loss of regulatory proteins, when mice are contrasted to humans.2,3 Moreover, contractile protein expression, critical to the excitation-contraction coupling process, seems to differ between the 2 species, as evidenced by their differing predominant myosin isoforms.2 Finally, evidence exists of significant phenotypic differences between mouse and human stem cells.3 Consequently, extrapolation of murine systems, particularly after induction of cardiovascular stress, becomes problematic when making interpretations of human HF pathophysiology. Therefore, large animal models of HF, which more closely approximate human physiology, function, and anatomy, are essential to develop the discoveries from murine models into clinical therapies and interventions for HF.

This review aims to summarize some of the more frequently used large animal models, which recapitulate the clinical HF phenotype arising from the common clinical etiologies of myocardial ischemia/infarction, ventricular overload states, and dilated cardiomyopathy. In terms of pharmacological and mechanical studies in these HF models, a brief perspective of how they contributed to the development of what are now considered pharmacological standards for HF treatment will be examined. Following which, a brief overview of how these HF models are now attempting to bridge the gap between new basic science discoveries and new clinical HF treatments will be considered.

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Models of Myocardial Ischemia/Myocardial Infarction

Canine Models of Ischemia/Myocardial Infarction

HF is frequently precipitated by myocardial ischemia, myocardial infarction (MI), or both. Historically, the adult canine model was the primary subject for investigating the effects of myocardial ischemia and MI. In what are now landmark studies, Reimer and Jennings used canine models to precisely identify the time course to irreversible myocardial injury with increasing periods of ischemia. Two key concepts were described in their reports: first, that myocardial ischemia caused myocyte death, which progressed in a “wavefront” pattern, moving from the subendocardium toward the epicardium, and second, that salvage of myocardial tissue occurred with early coronary reperfusion. Subsequent studies in canine models of myocardial ischemia by Przyklenk et al. further investigated the salvage of ischemic myocardium through the timely application of thrombolytic reperfusion. These studies built the foundation on which current reperfusion treatment guidelines for acute coronary syndromes were developed and provided proof of concept for thrombolytic therapy.

Despite these treatment advances for myocardial ischemia, injury can still occur, leading to long-term sequelae. Specifically, after MI, with or without subsequent reperfusion, invariable molecular, cellular, and interstitial changes occur, and can be manifested clinically as changes in size, shape, and function of the LV, which is termed myocardial remodeling. Over time, these initially compensatory changes lead to a deleterious cascade which serves as an impetus for the development of HF. The etiology of this transition is likely multifactorial, involving such processes as persistent activation of the neurohormonal axis, continued loss of functional myocytes via apoptosis, excessive loading conditions imposed on remaining viable myocardium, and alterations in the extracellular matrix of the myocardium. Along with myocardial remodeling, another process which has been found to occur after MI is infarct expansion, described as fully perfused but hypocontractile myocardium adjacent to the infarct extending to involve contiguous normal myocardium which undergoes progressive remodeling. Early infarct expansion after MI predicts late generalized LV dilation and progressive loss of LV function. Accordingly, large animal models of myocardial ischemia and MI have been used to investigate potential cellular and extracellular mechanisms which correlate to LV remodeling and infarct expansion, both of which give rise to the HF phenotype. For example, the canine MI model has been used to investigate abrogation of post-MI LV remodeling and examine the relation to the renin-angiotensin pathway. More specifically, Jugdutt and Menon explored the cardioprotective impact of valsartan, an angiotensin II type 1 receptor blocker, in a canine model of reperfused MI. Through temporary ligation of the left anterior descending coronary artery, pretreatment with valsartan was found to decrease infarct size, improve LV ejection fraction (EF) by almost 50%, limit infarct expansion and infarct thinning, and improve diastolic function after reperfused MI. A drawback of the canine model is the presence of significant collateral circulation in canine myocardium, making consistent degrees of myocardial injury difficult and potentially altering the post-MI course.

Ischemic Cardiomyopathy/Microembolization

The repetitive left-sided coronary artery microembolization model is another method to create myocardial ischemia, and subsequently an ischemic cardiomyopathy phenotype, in canines. In this model, dogs were subjected to multiple coronary artery embolic procedures serially performed over a 10-week period. After final embolizations the target LV EF of <35% was achieved with LV dilation. After the creation of reduced LV systolic function and dilation, progression of LV dysfunction occurred over the subsequent 3 months, accompanied by neurohormonal activation, decreased EF, and development of HF. The examination of several pharmacological targets and surgical therapies intended to treat LV failure have used the canine microembolization model. Examples include investigation of long-term therapy with enalapril, metoprolol, and digoxin on the progression of LV systolic dysfunction, examination of the hemodynamic effects of istaroxime, a lusino-inotropic agent being investigated in the treatment of acute decompensated HF, and study of the impact of a LV passive mechanical containment device on molecular and cellular abnormalities due to HF.

Although the canine microembolization model recapitulates the clinical phenotype of ischemic cardiomyopathy, it does so through multiple sites of infarction and remodeling as opposed to a single, discrete lesion of a large, focal MI. Consequently, the microembolization model is technically complex to produce, requiring serial surgical interventions. Malignant dysrhythmias can be a source of attrition and can be elicited due to the repetitive microembolization sessions. The multiplicity and heterogeneity of the myocardial response to the microembolizations can make interpretation of the biological responses difficult. Nevertheless, the model has been used to investigate novel pharmacological targets and surgical therapies for the treatment of HF and can resemble the clinical phenotype of ischemic cardiomyopathic disease.

Porcine and Ovine Models of MI

Although numerous discoveries regarding myocardial ischemia and MI have been made with the use of canine models, several confounding factors including collateral coronary circulation contributed to a transition to alternative animal species, including pigs and sheep, in the study of myocardial ischemia and MI. Consistent coronary arterial anatomy, lack of preformed collateral vessels, and the ability to create infarctions of predictable size and location make both pigs and sheep reasonable choices for studying myocardial ischemia and postinfarction LV remodeling. Furthermore, porcine hearts exhibit coronary artery anatomy and gross anatomic structure very similar to that of humans and have been the subject of translational studies.

Pig MI Models

Quantitative evaluation of the anatomy and distribution of swine coronary arteries has found scant coronary collaterals,
which were primarily localized to the mid myocardium and subendocardium, unlike the extensive epicardial collaterals found in dogs.\textsuperscript{13} Given these findings, pigs have been used as models of myocardial ischemia and MI in the setting of graduated treadmill exercise training and increasing oxygen demand.\textsuperscript{10} Several of these studies have used ameroid constriction as a means of establishing initial high-grade coronary stenosis followed by occlusion.\textsuperscript{10} Although progressive occlusion of a coronary artery can yield LV dysfunction, the HF phenotype is most effectively produced by total coronary artery occlusion. Acute coronary occlusion depresses LV function and prompts neurohormonal activation, thus satisfying several criteria characteristic of the HF phenotype. Porcine models of MI have been used to study infarct expansion and LV remodeling in the post-MI setting.\textsuperscript{16} For example, MI induction in adult pigs facilitated placement of radio-opaque markers which quantified reproducible, progressive infarct expansion and characteristics of the borderzone.\textsuperscript{7} Markovitz et al\textsuperscript{21} used selective coronary artery ligation in a sheep MI model to demonstrate changes similar to those seen in patients with HF, namely, progressive LV remodeling and aneurysm formation.

Limitations of working with sheep models include issues of zoonotic diseases. Sheep, being domesticated ruminants, also have gastrointestinal anatomy and thoracic contours that can make certain imaging approaches difficult, specifically ultrasonic imaging necessitates an invasive approach as opposed to transthoracic imaging suitability.\textsuperscript{7,20}

**Models of Overload**

**Volume Overload**

A common approach to induce a volume overload state in a large animal model is through chordal rupture of the mitral valve apparatus.\textsuperscript{23–28} The resultant MR creates chronic volume overload, leading to significant LV dilation and subsequent HF (Figure 3). Roughly 2 decades ago a closed-chest canine model of MR was created using arterially placed grasping forceps to disrupt mitral chordae in anesthetized dogs.\textsuperscript{24} This model served as the basis for later studies, which achieved consistent mitral regurgitant fractions >50%, LV dilation, neurohormonal activation, and volume overload hypertrophy, thus recapitulating the volume overload HF phenotype.\textsuperscript{25–27} Abnormalities at the cellular level associated with developing LV dysfunction, such as alterations in myocyte contractile function, have been elucidated through canine models of chordal rupture-induced MR.\textsuperscript{23,26} Subsequent mitral valve replacement has been found to normalize these cellular alterations.\textsuperscript{23} The progressive neurohormonal
activation achieved by the canine chronic MR model has allowed investigation of the effects of angiotensin II type 1 and β-receptor blockade on LV failure.26,28 For example, an important finding by Tsutsui et al was that chronic MR dogs treated with β-receptor antagonists had substantially improved contractile function and increased contractile elements in LV myocardial specimens in comparison with controls.26 Using this model, an interaction between β-receptor activation and release of angiotensin into the myocardial interstitium was demonstrated.28 These studies provided a critical insight into the mechanisms by which β-receptor antagonism may be operative in the context of volume overload induced HF.

Pressure Overload
LV pressure overload causes a compensatory increase in LV mass; ie, LV hypertrophy. Features of pressure overload induced LV hypertrophy are decreased LV compliance and excessive collagen accumulation.29,30 The myocardium of patients with severe LV pressure overload hypertrophy have significant myocardial matrix accumulation (ie, fibrosis).29 A model of pressure overload LV hypertrophy was created in a nonhuman primate in the landmark work of Weber and Janicki et al.29 Significant LV hypertrophy and fibrosis in these animals was observed, similar to findings in patients with aortic stenosis.30 Thus, this study and others provided an important causal link between changes in the extracellular matrix and progressive LV diastolic dysfunction.29,31,32 The work of Weber et al also provided a model in which to target the myocardial extracellular matrix in future HF studies.31,32 Although pressure overload LV hypertrophy is an important cause of HF, there are few studies that have used a large animal model of this condition. One study that has attempted to recapitulate the pressure overload HF phenotype used aortic banding in canines to study LV remodeling mechanisms.31 Other methods to create a pressure overload large animal model have included renal artery constriction and creation of aortic stenosis.33,34 The reduced LV relaxation and filling, and increased LV stiffness, created in these models would make them well suited for the investigation of diastolic dysfunction, a likely precursor to LV failure in this setting.

Figure 2. Sheep MI Model. A, Sheep heart as exposed through a left thoracotomy. B, The LV is measured from apex to base. The left anterior descending (LAD) coronary artery and any of its diagonal branches that pass below an imaginary line drawn parallel to the base of the heart at a level 40% of the distance from apex to base are ligated. C, The anteroapical ischemic zone is immediately apparent. The resulting infarct typically involves 21% to 24% of the LV mass and leads to progressive LV dilatation and loss of global function. D, Photograph of a sheep anteroapical infarct 1 hour after coronary ligation. Courtesy of R.C. Gorman, MD, Cardiothoracic Surgery, University of Pennsylvania.
Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is defined by structural hallmarks of LV dilation and increased LV chamber radius-to-wall thickness ratio, resulting in increased LV wall stress. The most well-characterized large animal model of DCM is the pacing induced tachycardia model. First described by Whipple et al in 1962, this model was used to demonstrate pacemaker-induced chronic tachycardia superimposed on normal myocardium results in the development of LV failure. A number of studies have used rapid pacing, applying the method to dogs, pigs, and sheep, to create DCM models for the investigation of LV systolic dysfunction, myocyte contractile dysfunction, and neurohormonal activation, all critical features of HF. One important observation is that pacing-induced DCM causes alterations in the neurohormonal system in a time-dependent fashion (Figure 4), with early elevation and subsequent plateau of plasma catecholamine levels in contrast to elevations of endothelin and renin, which tend to occur later, in more advanced stages of LV dysfunction. These findings are consistent with clinical observations in which elevated plasma endothelin levels occurred only in those patients with moderate to severe HF. Furthermore, the neurohormonal marker atrial natriuretic peptide was identified in the pacing model, contributing to the establishment of atrial natriuretic peptide as a diagnostic marker in patients with HF. Rapid pacing has also been shown to induce deteriorations in isolated myocyte function, with blunted response to ionotropic stimuli and diminishment of β-receptor density. Post-β-receptor abnormalities, particularly with regard to calcium homeostasis and adenylyl cyclase activity, have also been demonstrated in the rapid pacing model. Analogous to elevations in plasma endothelin levels, pacing-induced changes in β-receptor density and function parallel those observed in patients with HF. The rapid pacing model has been used to identify contributory pathways for the progression to LV systolic dysfunction. For example, the use of angiotensin-converting enzyme inhibition has been shown to normalize of β-adrenergic receptor function and enhance myocardial collagen support. This laboratory has used a DCM model in pigs to assess the effects of angiotensin-converting enzyme inhibition and angiotensin II receptor (type 1) blockade on LV function, systemic hemodynamics, and neurohormonal activation. This combinatorial treatment showed beneficial additive effects on LV function and structure and neurohor-

Figure 3. Left, Shaded surface display of right ventricle and LV of endo- and epicardial surfaces at end-diastole in a dog before (normal, top left) and after MR (bottom left) using MRI in the dog. Note the nonuniform dilatation of the LV cavity and the reduction in volume of the right ventricle as well as expansion of the LV into the right ventricle cavity. Adapted. Right, End-diastolic volume (EDV) calculated angiographically is shown at baseline (B), at acute MR (AMR), and after mitral regurgitation had been present for 3 months (MR3) in canines. EDV was significantly increased at 3 months in comparison with baseline and AMR. Reproduced.

Figure 4. Serial changes in plasma norepinephrine, atrial natriuretic factor (ANF), and cGMP in control dogs (Y), dogs with long-term rapid pacing (A), and dogs with long-term pacing and concomitant angiotensin-converting enzyme inhibition (●). Top, In pacing groups, norepinephrine significantly increased from baseline values after 1 week and seemed to plateau with long-term tachycardia. Plasma norepinephrine was significantly lower with angiotensin-converting enzyme inhibition compared with pacing only group. Middle, ANF levels were significantly increased after 1 week of rapid pacing, remaining elevated through the 4 week protocol. Bottom, angiotensin-converting enzyme inhibition was found to attenuate cGMP elevation with long-term rapid pacing. Reproduced with permission.
monal activation. These past observations in large animal models of DCM provided preclinical support and subsequently catalyzed the large-scale clinical trial using combined angiotensin-converting enzyme and angiotensin II receptor (type 1) blockade in HF. Other studies have investigated novel surgical techniques through pacing models of DCM. For example, a rigid transventricular brace, used to decrease the radii of dilated LV chambers, was found to reduce LV wall stress and improve LV systolic function.

Advantages of the rapid pacing model include neurohormonal alterations consistent with those observed in humans, generation of predictable degrees of LV dilation and pump dysfunction, and the ability to test pharmacological strategies aimed at attenuating progression of LV dysfunction to HF. However, it should be recognized that rapid pacing models fail to manifest the complete spectrum of HF. Although rapid pacing induces LV dilation and dysfunction consistent with what is found in patients with DCM, the resultant myocardial structure is distinctly different from that which is observed in HF due to other etiologies, such as myocardial ischemia and volume overload. Finally, global LV function partially recovers on cessation of pacing, a feature unique to the pacing model of HF.

Developing New Therapeutic Targets in HF
Gene Therapy
As the morbidity and cost of HF have continued to increase, so has the understanding of cellular and molecular derangements which take place in HF. This increasing knowledge combined with the urgency to discover and develop novel and improved therapeutic strategies for HF has led to targeting molecular entities involved in HF pathogenesis through gene therapy. Efforts to create HF therapies targeting molecular causes of myocardial failure have focused on areas such as regulation of cardiomyocyte calcium handling. For example, Kaye et al used a sheep model of rapid pacing-induced DCM to develop a percutaneous means of myocardial gene delivery of a mutant form of the regulatory protein phospholamban, reporting improved cardiac function compared with controls. In a different study Kawase et al examined the therapeutic potential of gene delivery in a pig model of volume overload HF. The study observed improved LV contractile performance and myocardial remodeling 2 months after SERCA2a, the cardiac isoform of a family of calcium ATPases, gene delivery administered by antegrade epicardial coronary artery infusion. The first human HF gene therapy trials have now been initiated on patients with HF receiving SERCA2a via myocardial gene delivery, providing an example of how large animal models serve a crucial step in the translation of basic science into clinical application.

Stem Cells
Advances in the field of cellular therapies have created a new avenue of potential HF treatments, specifically in area of stem cell research. Stem cells derived from various tissues have been introduced into the post-MI myocardium in efforts to attenuate post-MI LV remodeling. Initial studies using murine models reported dramatic results of stem cells having the ability to localize to the heart and purported to yield new myocardium. However, more recent clinical studies using mesenchymal stem cells have failed to demonstrate significant effects on post-MI LV remodeling and function. The reasons for the failure of translation from basic stem cell studies to the clinical context are multifactorial, but likely include a lack of consensus regarding optimal stem cell type and preparation, delivery method, delivery location, and cell concentration. Large animal models will play a critical role in defining these factors (Table). For example, the relative

### Table. Large Animal Models of Mesenchymal Stem Cell Cardiac Therapy Effects on Post-MI LV Remodeling

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal Model</th>
<th>Dose (x10^6)</th>
<th>Delivery Method</th>
<th>Duration of Study, mo</th>
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<td>3</td>
<td>Decreased EF</td>
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<tr>
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<tr>
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<td>100</td>
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<td>2</td>
<td>Increased EF</td>
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Dixon and Spinale Models of Heart Failure
efficacy of mesenchymal stem cells has been evaluated in the pig MI model, with reports of improved LV EF after myocardial delivery of mesenchymal stem cells at the time of MI. Other studies have reported decreased MI expansion in pig and sheep MI models with mesenchymal stem cells delivered into the myocardium within 72 hours of MI and attenuation of EF deterioration with delivery 1 month post-MI. Alternatively, intracoronary and systemic delivery of mesenchymal stem cells have also been examined, further exemplifying the utility of large animal models in clarifying variables in stem cell therapies. It is likely that these translational studies in large animal models will be necessary if the tremendous potential suggested by rodent studies is to be realized clinically.

Devices and Mechanical Support
A number of innovative devices aimed at improving LV systolic function and/or cardiac output in patients with HF have been created and refined through large animal models. From comparisons of early LV assist devices with the development of a totally implantable biventricular assist system, large animals have served an integral role in groundbreaking advances in cardiac destination therapies. The adaptation of such devices for neonatal and pediatric use has also been possible through large animal models. The development of minimally invasive devices to unload pressure from the failing LV have also used large animal models. For example, Haithcock et al used a canine microembolization model of HF to demonstrate the benefits of LV unloading, establishing the basis for a percutaneously placed continuous aortic flow augmentation device, which is now in clinical trial. Other work has been directed toward cardiac restraint devices, which are surgically placed around the heart itself to arrest post-MI LV remodeling. Specifically, Blom et al used a sheep MI model to investigate a polyester weave device, reporting beneficial modifications of LV and myocyte remodeling. Moreover, these preclinical studies resulted in translation of this device into application in patients with severe LV dilation and dysfunction.

In other efforts to improve cardiac function in patients with HF, cardiac resynchronization therapy has been brought to the clinical arena through the use of large animal models. For example, Chakir et al used a canine rapid-pacing model to demonstrate reduced myocyte apoptosis and improved stress-response molecular signaling with cardiac resynchronization therapy. Further advances and improvements in HF device therapies will surely depend on large animal models to ensure the safety and efficacy of these therapeutic options.

Pharmacological Treatments
Another field where large animal models have provided a bridge between basic science and clinical applications is the creation of new drug therapies for HF, such as targeting the extracellular matrix. For example, using the canine microembolization model and the pig MI model a pharmacological matrix metalloproteinase inhibitor was shown to attenuate the progression of LV remodeling. These studies provided the impetus for the initiation of a clinical study in the post-MI setting. Another pharmacological agent that was brought to the clinical arena with the help of large animal studies is levosimendan, a myofilament calcium sensitizer, which has been found to have positive ionotropic effects in acute and decompensated HF. Levosimendan was used in the canine pacing-induced DCM model, finding favorable alterations in hemodynamics and positive inotropic and lusitropic effects. With respect to device driven therapies, the microembolization model has been used to investigate electric signals delivered to the myocardium, reporting improved LV systolic function and favorably influenced LV remodeling. Thus, as researchers continue to explore possible pharmacological and mechanical HF treatments, large animal models will undoubtedly play a key role in the process.

Summary
Tremendous information regarding cardiac structure and development has been gained from genomics and subsequent transgenesis. Likewise, the burgeoning field of proteomics promises to yield an explosion of knowledge at the protein level. However, despite these remarkable advances at the molecular and protein levels, commensurate gains in new clinically applicable HF treatments seem to be lacking in comparison, calling attention to the chasm between basic research and bedside medicine. Contributory factors for this failure of translational research include reduced emphasis on integrative physiology, infrastructure, and difficulties in animal model selection. First, PhD training too often places lesser import on integrative physiology and human research. Second, new research facilities are too often omitting the considerable space and resources demanded by large animal experimental facilities. Although murine facilities lend themselves to streamlined efficiency, this is not the nature of large animal laboratories. A multidisciplinary team of scientists, surgeons, and clinicians are required to carry out the rigorous work of large animal studies to produce truly translational research. Third, it must be recognized that there is no perfect animal model of HF and careful individualized analysis is required to determine the appropriate model for the specific issue being investigated. Large animal models recapitulating the clinical HF phenotype and translating basic science to clinical applications have successfully traveled the journey from bench to bedside. Undoubtedly, large animal models of HF will continue to play a crucial role in the elucidation of biological pathways involved in HF and the development and refinement of HF therapies.

Disclosures
None.

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