Creation of clinically relevant model of chronic heart failure: Application of multi-modality imaging to define physiology

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Heart failure (HF) remains a major cause of mortality and morbidity in the world.¹ Despite significant improvement in both medical and surgical therapies for HF, the mortality rate persists in excess of 50% after 5 years.² Ischemic heart disease remains a leading cause of HF, and has a complex and incompletely understood pathophysiology with acute ischemic injury evolving to progressive left ventricular (LV) dysfunction and structural remodeling. These chronic functional and structural changes are associated with compensatory neurohormonal and metabolic alterations.

The complex natural progress of atherosclerosis in humans can lead to either acute or slowly progressive coronary occlusion with the initial ischemic insult not easily emulated in an animal model. Pre-clinical approaches and large animal models to mimic ischemic heart disease have included single and multi-step catheter-based and surgical interventions.^{3–17} Generally, these interventions are performed in normal animals without the same pathophysiological substrate that leads to atherosclerosis or modulates the repair processes in humans. Therefore, the initial injury, repair, and remodeling processes may not be completely

comparable to the clinical scenario. However, robust large animal models have tried to reproduce the fundamental characteristics of the process of repair and LV remodeling, including changes in LV geometry and dilatation, eccentric hypertrophy, infarct expansion, alterations in regional and global LV systolic and diastolic performance and functional reserve under stress, alterations in LV mass, and changes in regional wall thickness.⁷ Ideally, these animal models should have a mortality rate that is comparable to the clinical scenario and be highly reproducible in order to provide proper predicative value for clinical investigations into the pathophysiological mechanisms, and evaluation of novel therapeutics and interventions.

While several large animal models have been employed to model ischemic heart disease in humans (including canine, porcine, and ovine), the coronary and gross cardiac anatomy in swine is fairly equivocal to humans. Unlike canine models, that have a significant native collateral circulation, swine have less native preformed collateral circulation in the mid-myocardium and sub-endocardium.¹⁸ Therefore, the porcine model is frequently used to test devices and therapies in models of acute ischemic heart disease, as well as models of chronic ventricular remodeling post-ischemic injury, and HF. The size of swine also allow for the use of standardized clinical investigational tools and equipment, including advanced clinical imaging systems. Recent reviews have summarized the animal models of HF,^{5,7,19} and some have even focused specifically on porcine models.⁴

Large animal models of HF with preserved ejection fraction (HFpEF) have been more difficult to establish partly due to the incomplete pathological understanding of HFpEF.²⁰ There is one proposed swine model that is thought to mimic HFpEF that involves staged banding of

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the aorta.²¹ Other investigators recently have developed an ovine model that may approximate the conditions of HFpEF.¹⁰ As such, the majority of pre-clinical studies focus on systolic HF and employ permanent or transient surgical ligation of coronary arteries to produce a HF model with decreased ejection fraction. These models are highly dependent on the size of the ischemic insult. Percutaneous approaches are an alternative to surgical models where inflammation and development of fibrotic tissue at the surgical site can interfere with imaging techniques. However, these percutaneous models can have reduced reproducibility, as intracoronary placement of the occluding balloon, coil, or stent can be highly dependent on the gross coronary anatomy and navigation through the coronary arteries under fluoroscopy. Ischemia-reperfusion via balloon angioplasty provides a means to emulate acute ischemic injury and subsequent remodeling following revascularization.^{15,17,22} However, further to the placement of the balloon and subsequent size of ischemic zone, fatal arrhythmias during the reperfusion period can contribute to a high percentage of the overall mortality. Investigators have devised other percutaneous approaches using coronary microembolization, intracoronary thrombotic coil deployment,¹³ and placement of bottleneck stents¹⁶ to produce ischemic injury with decreases in LV EF and mortality between 13% and 37%.

Surgical ligation models have the advantages of a reduction in overall procedure time, improved accuracy in the selection of the location of the ligation, and reproducibility of the extent of ischemic injury. In a permanent surgical occlusion model, the level (proximal, distal, and mid) and location (left anterior descending (LAD) vs left circumflex (LCX) or branches) have been shown to dramatically alter the MI size (0%-21%) and mortality rate (0%->70%).^{6,14} While a more distal ligation and subsequent smaller MI size serves to ensure a high survival rate, these smaller infarcts result in minimal LV remodeling and do not induce significant HF.¹⁴ Ameroid constrictor models have been widely used, and conceptually due to the slow occlusion of the coronary artery, result in a low attrition rate (approximately 26%).⁴ This surgical intervention is well established and leads to a classic model of hibernating myocardium.^{4,11,12,23}

Teramoto and colleagues³ previously reported a swine model of HF induced by permanent ligation on the distal portion of the LAD, followed by proximal placement of an ameroid constrictor to occlude the proximal portion. This study was able to demonstrate a high survival rate out to 4-month post-surgery (75%), and characterized LV remodeling in the setting of reduced EF, and increased end-diastolic and end-systolic

volumes with initial development of fibrosis in the remote regions.

In this issue of the *Journal of Nuclear Cardiology*, Tarkia and colleagues, recapitulated the porcine model of staged coronary occlusion initially reported by Teramoto³ and characterized the LV remodeling process structurally, functionally, and metabolically by PET/CT imaging with [¹⁵O]water and [¹¹C]acetate at 3-month post-surgical intervention. They apply PET/CT imaging, as well as echocardiography to understand the changes in myocardial rest/stress perfusion, metabolism, wall stress, regional and global work, and efficiency in the remote areas of heart following myocardial infarction. Their utilization of clinically available imaging tools creates an easily translatable methodology between pre-clinical and clinical in predictions of HF outcomes. Additionally, due to the non-invasive technique of these imaging tools, their model and imaging approach can provide a means to evaluate the progression of HF and to quantify the temporal changes in flow and metabolism. In addition to the information provided on perfusion and metabolic outcomes, additional imaging could be applied to interrogate regional activation of critical receptors or enzymes within the myocardium,²⁴⁻²⁸ neurohormonal changes,²⁹⁻³³ along with regional changes in myocardial hypoxia,³⁴ apoptosis,^{35,36} necrosis,³⁷ and fibrosis.³⁸

Unfortunately, the current study reported a high attrition (overall survival rate of 26%) with a major cause of death attributable to lethal arrhythmias during the peri-operative period. However, chronic telemetry was not performed in these studies to establish an arrhythmic cause of death during the chronic experimental period. Resting flow and inducible ischemia are critical parameters with regard to assessing risk for arrhythmias in this model, although these risk factors were not critically evaluated in the current study. It is not clear if the late deaths were due to the primary distal injury and substrate for reentrant ventricular tachycardia, or resting ischemia, or stress-induced ischemia associated with activity of these animals and ischemia-induced arrhythmia, or possibly even pump failure. The use of telemetry, additional imaging of the animals at an earlier time point, or evaluation of the infarct size ex vivo after death may have helped to determine the cause of death in these animals.

However, the researchers were able to demonstrate robust endpoints for characterization of LV remodeling at the 3-month follow-up time point. The overall mass of the LV was tending to an increase as measured by in vivo contrast x-ray CT angiography in the pigs with HF vsd controls (HF: 193 ± 42; control: 160 ± 29 g, $P = .07$), and this corresponded to an increase in LV end-diastolic volumes (HF: 252 ± 84 mL; control: 145 ± 17 mL, $P = .003$) and end-systolic volumes (HF: 154 ± 68 mL;

control: 53 ± 7 mL, $P = .001$). At the experimental endpoint, these animals did not have significant fibrosis in the remote zone; however, the myocardium in these remote regions displayed a significant increase in cardiomyocyte diameter. Functionally, these animals demonstrated a decreased LVEF, cardiac output, and global LV work, with an increase in systolic wall stress. The novelty in this study, is the application of [^{11}C]acetate to this clinically relevant porcine model of HF. The primary application of [^{11}C]acetate was to measure oxidative metabolism in the context of remodeling and changes in regional LV energetics, and to determine mechanical efficiency or the increase in energy expenditure in relation to work.³⁹ As applied by these investigators, [^{11}C]acetate could be used to assess the temporal progression of the metabolic LV remodeling, in association with the functional remodeling that leads to HF. However, in this study, [^{11}C]acetate was studied only at the 3-month time point, limiting the evaluation of metabolic and/or functional remodeling throughout the period that led to progressive HF. The investigators were able to demonstrate that although myocardial perfusion in the remote zone was the same at both rest and stress in the HF animals compared to controls, the global myocardial efficiency was decreased while the regional efficiency in the remote area was increased.

With new therapies currently under testing for treatment of HF,⁴⁰ the development of clinically relevant animal models that can recapitulate the pathology of human ischemic heart disease and techniques that can be used to monitor temporal progression are of increased importance. We look forward to further pre-clinical investigation with this porcine model with the application of conventional physiological imaging, as well as more advanced molecular imaging modalities in order to better define the underlying pathophysiology of HF. The proposed model and multi-modality imaging can also be used to evaluate novel therapeutics designed to reduce the adverse remodeling following ischemic injury, and to prevent and treat associated HF.

Conflict of interest

The authors have no conflict of interest to disclose.

References

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorgiade M. The global health and economic burden of hospitalizations for heart failure: Lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;63:1123-33.

2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics—2013 update: A report from the American heart association. *Circulation* 2013;127:e6-245.
3. Teramoto N, Koshino K, Yokoyama I, Miyagawa S, Zeniya T, Hirano Y, Fukuda H, Enmi J, Sawa Y, Knuuti J, Iida H. Experimental pig model of old myocardial infarction with long survival leading to chronic left ventricular dysfunction and remodeling as evaluated by pet. *J Nucl Med* 2011;52:761-8.
4. Ishikawa K, Ladage D, Takewa Y, Yaniz E, Chen J, Tilemann L, Sakata S, Badimon JJ, Hajjar RJ, Kawase Y. Development of a preclinical model of ischemic cardiomyopathy in swine. *Am J Physiol Heart Circ Physiol* 2011;301:H530-7.
5. Monnet E, Chachques JC. Animal models of heart failure: What is new? *Ann Thorac Surg* 2005;79:1445-53.
6. Yarbrough WM, Spinale FG. Large animal models of congestive heart failure: A critical step in translating basic observations into clinical applications. *J Nucl Cardiol* 2003;10:77-86.
7. Houser SR, Margulies KB, Murphy AM, Spinale FG, Francis GS, Prabhu SD, Rockman HA, Kass DA, Molkenstein JD, Sussman MA, Koch WJ. American Heart Association Council on Basic Cardiovascular Sciences CoCC, Council on Functional G, Translational B. Animal models of heart failure: A scientific statement from the American heart association. *Circ Res* 2012;111:131-50.
8. Heusch G, Skyschally A, Schulz R. The in situ pig heart with regional ischemia/reperfusion—ready for translation. *J Mol Cell Cardiol* 2011;50:951-63.
9. Wu JC, Yun JJ, Dione DP, Heller EN, Deckelbaum LI, Sinusas AJ. Severe regional ischemia alters coronary flow reserve in the remote perfusion area. *J Nucl Cardiol* 2000;7:43-52.
10. Dayan V, Sotelo V, Delfina V, Delgado N, Rodriguez C, Suanes C, Langhain M, Ferrando R, Touriño C, Benesh A. Ischemia-induced model of diastolic dysfunction in sheep. *J Investig Surg* 2014. doi: 10.3109/08941939.2014.970303.
11. Mills I, Fallon JT, Wrenn D, Sasken H, Gray W, Bier J, Levine D, Berman S, Gilson M, Gewirtz H. Adaptive responses of coronary circulation and myocardium to chronic reduction in perfusion pressure and flow. *Am J Physiol* 1994;266:H447-57.
12. Fallavollita JA, Perry BJ, Canty JM Jr. 18f-2-deoxyglucose deposition and regional flow in pigs with chronically dysfunctional myocardium. Evidence for transmural variations in chronic hibernating myocardium. *Circulation* 1997;95:1900-9.
13. Dib N, Diethrich EB, Campbell A, Gahremanpour A, McGarry M, Opie SR. A percutaneous swine model of myocardial infarction. *J Pharmacol Toxicol Methods* 2006;53:256-63.
14. Munz MR, Faria MA, Monteiro JR, Aguas AP, Amorim MJ. Surgical porcine myocardial infarction model through permanent coronary occlusion. *Comp Med* 2011;61:445-52.
15. Angeli FS, Shapiro M, Amabile N, Orcino G, Smith CS, Tacy T, Boyle AJ, Chatterjee K, Glantz SA, Grossman W, Yeghiazarians Y. Left ventricular remodeling after myocardial infarction: Characterization of a swine model on beta-blocker therapy. *Comp Med* 2009;59:272-9.
16. Rissanen TT, Nurro J, Halonen PJ, Tarkia M, Saraste A, Rannankari M, Honkonen K, Pietila M, Leppanen O, Kuivanen A, Knuuti J, Yla-Herttuala S. The bottleneck stent model for chronic

- myocardial ischemia and heart failure in pigs. *Am J Physiol Heart Circ Physiol* 2013;305:H1297-308.
17. McCafferty K, Forbes S, Thiemermann C, Yaqoob MM. The challenge of translating ischemic conditioning from animal models to humans: The role of comorbidities. *Dis Models Mech* 2014;7:1321-33.
 18. Weaver ME, Pantely GA, Bristow JD, Ladley HD. A quantitative study of the anatomy and distribution of coronary arteries in swine in comparison with other animals and man. *Cardiovasc Res* 1986;20:907-17.
 19. Klocke R, Tian W, Kuhlmann MT, Nikol S. Surgical animal models of heart failure related to coronary heart disease. *Cardiovasc Res* 2007;74:29-38.
 20. Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JG, Cody RJ, Chioncel O, Collins SP, Dunnmon P, Filippatos G, Lefkowitz MP, Marti CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopoulou VV, Gheorghiade M. Developing therapies for heart failure with preserved ejection fraction: Current state and future directions. *JACC Heart Fail* 2014;2:97-112.
 21. Yarbrough WM, Mukherjee R, Stroud RE, Rivers WT, Oelsen JM, Dixon JA, Eckhouse SR, Ikonomidis JS, Zile MR, Spinale FG. Progressive induction of left ventricular pressure overload in a large animal model elicits myocardial remodeling and a unique matrix signature. *J Thorac Cardiovasc Surg* 2012;143:215-23.
 22. Vilahur G, Casani L, Pena E, Juan-Babot O, Mendieta G, Crespo J, Badimon L. Hmg-coa reductase inhibition prior reperfusion improves reparative fibrosis post-myocardial infarction in a preclinical experimental model. *Int J Cardiol* 2014;175:528-38.
 23. Giordano C, Thorn SL, Renaud JM, Al-Atassi T, Boodhwani M, Klein R, Kuraitis D, Dwivedi G, Zhang P, Dasilva JN, Ascah KJ, Dekemp RA, Suuronen EJ, Beanlands RS, Ruel M. Preclinical evaluation of biopolymer-delivered circulating angiogenic cells in a swine model of hibernating myocardium. *Circ Cardiovasc Imaging* 2013;6:982-91.
 24. Park-Holohan SJ, Asselin MC, Turton DR, Williams SL, Hume SP, Camici PG, Rimoldi OE. Quantification of [11c]gb67 binding to cardiac alpha1-adrenoceptors with positron emission tomography: Validation in pigs. *Eur J Nucl Med Mol Imaging* 2008;35:1624-35.
 25. Sahul ZH, Mukherjee R, Song J, McAteer J, Stroud RE, Dione DP, Staib L, Papademetris X, Dobrucki LW, Duncan JS, Spinale FG, Sinusas AJ. Targeted imaging of the spatial and temporal variation of matrix metalloproteinase activity in a porcine model of postinfarct remodeling: Relationship to myocardial dysfunction. *Circ Cardiovasc Imaging* 2011;4:381-91.
 26. Lortie M, DaSilva JN, Kenk M, Thorn S, Davis D, Birnie D, Beanlands RS, deKemp RA. Analysis of (r)- and (s)-[(11c)]rolipram kinetics in canine myocardium for the evaluation of phosphodiesterase-4 with pet. *Mol Imaging Biol* 2012;14:225-36.
 27. Fukushima K, Bravo PE, Higuchi T, Schuleri KH, Lin X, Abraham MR, Xia J, Mathews WB, Dannals RF, Lardo AC, Szabo Z, Bengel FM. Molecular hybrid positron emission tomography/computed tomography imaging of cardiac angiotensin ii type 1 receptors. *J Am Coll Cardiol* 2012;60:2527-34.
 28. Mozid AM, Holstensson M, Choudhury T, Ben-Haim S, Allie R, Martin J, Sinusas AJ, Hutton BF, Mathur A. Clinical feasibility study to detect angiogenesis following bone marrow stem cell transplantation in chronic ischaemic heart failure. *Nucl Med Commun* 2014;35:839-48.
 29. Fallavollita JA, Heavey BM, Luisi AJ Jr, Michalek SM, Baldwa S, Mashtare TL Jr, Hutson AD, Dekemp RA, Haka MS, Sajjad M, Cimato TR, Curtis AB, Cain ME, Canty JM Jr. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. *J Am Coll Cardiol* 2014;63:141-9.
 30. Fallavollita JA, Banas MD, Suzuki G, deKemp RA, Sajjad M, Canty JM Jr. 11c-meta-hydroxyephedrine defects persist despite functional improvement in hibernating myocardium. *J Nucl Cardiol* 2010;17:85-96.
 31. Luisi AJ Jr, Suzuki G, Dekemp R, Haka MS, Toorongian SA, Canty JM Jr, Fallavollita JA. Regional 11c-hydroxyephedrine retention in hibernating myocardium: Chronic inhomogeneity of sympathetic innervation in the absence of infarction. *J Nucl Med* 2005;46:1368-74.
 32. Luisi AJ Jr, Fallavollita JA, Suzuki G, Canty JM Jr. Spatial inhomogeneity of sympathetic nerve function in hibernating myocardium. *Circulation* 2002;106:779-81.
 33. Jain KK, Hauptman PJ, Spertus JA, Kennedy KF, Bateman TM, Jacobson AF, Stolker JM. Incremental utility of iodine-123 meta-iodobenzylguanidine imaging beyond established heart failure risk models. *J Cardiac Fail* 2014;20:577-83.
 34. Handley MG, Medina RA, Mariotti E, Kenny GD, Shaw KP, Yan R, Eykyn TR, Blower PJ, Southworth R. Cardiac hypoxia imaging: Second-generation analogues of 64cu-atrm. *J Nucl Med* 2014;55:488-94.
 35. Taki J, Higuchi T, Kawashima A, Fukuoka M, Kayano D, Tait JF, Matsunari I, Nakajima K, Kinuya S, Strauss HW. Effect of post-conditioning on myocardial 99mtc-annexin-v uptake: Comparison with ischemic preconditioning and caspase inhibitor treatment. *J Nucl Med* 2007;48:1301-7.
 36. Johnson LL, Schofield L, Donahay T, Narula N, Narula J. 99mtc-annexin v imaging for in vivo detection of atherosclerotic lesions in porcine coronary arteries. *J Nucl Med* 2005;46:1186-93.
 37. Tahara N, Zandbergen HR, de Haas HJ, Petrov A, Pandurangi R, Yamaki T, Zhou J, Imaizumi T, Slart RH, Dyszlewski M, Scarbelli T, Kini A, Reutelingsperger C, Narula N, Fuster V, Narula J. Noninvasive molecular imaging of cell death in myocardial infarction using 111in-gsao. *Sci Rep* 2014;4:6826.
 38. Velikyan I, Rosenstrom U, Estrada S, Ljungvall I, Haggstrom J, Eriksson O, Antoni G. Synthesis and preclinical evaluation of 68ga-labeled collagelin analogs for imaging and quantification of fibrosis. *Nucl Med Biol* 2014;41:728-36.
 39. Beanlands RS, Bach DS, Raylman R, Armstrong WF, Wilson V, Montieth M, Moore CK, Bates E, Schwaiger M. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 1993;22:1389-98.
 40. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Investigators P-H Committees. Angiotensin-neprilysin inhibition vs enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.