

Simultaneous determination of dynamic cardiac metabolism and function using PET/MRI

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Received Sep 13, 2017; accepted Apr 13, 2018

doi:10.1007/s12350-018-1287-7

Background. Cardiac metabolic changes in heart disease precede overt contractile dysfunction. However, metabolism and function are not typically assessed together in clinical practice. The purpose of this study was to develop a cardiac positron emission tomography/magnetic resonance (PET/MR) stress test to assess the dynamic relationship between contractile function and metabolism in a preclinical model.

Methods. Following an overnight fast, healthy pigs (45–50 kg) were anesthetized and mechanically ventilated. ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) solution was administered intravenously at a constant rate of 0.01 mL/s for 60 minutes. A cardiac PET/MR stress test was performed using normoxic gas (F₁O₂ = .209) and hypoxic gas (F₁O₂ = .12). Simultaneous cardiac imaging was performed on an integrated 3T PET/MR scanner.

Results. Hypoxic stress induced a significant increase in heart rate, cardiac output, left ventricular (LV) ejection fraction (EF), and peak torsion. There was a significant decline in arterial SpO₂, LV end-diastolic and end-systolic volumes in hypoxia. Increased LV systolic function was coupled with an increase in myocardial FDG uptake (K_i) during hypoxic stress.

Conclusion. PET/MR with continuous FDG infusion captures dynamic changes in both cardiac metabolism and contractile function. This technique warrants evaluation in human cardiac disease for assessment of subtle functional and metabolic abnormalities. (J Nucl Cardiol 2019;26:1946–57.)

Key Words: Physiology of LV/RV function • metabolic • MRI • PET

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s12350-018-1287-7>) contains supplementary material, which is available to authorized users.

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Funding Research support was provided in part by the University of Wisconsin-Madison School of Medicine and Public Health Department Research and Development Funds from the Departments of Pediatrics (Eldridge), Medicine (Goss) and Radiology (McMillan), as well as additional funding from the Wisconsin Alumni Research Foundation (Eldridge). Kara Goss and portions of the project are

supported by the University of Wisconsin Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), Grant NIH UL1TR000427 (PI Drescher; 4KL2TR000428-10).

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1071-3581/\$34.00

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Abbreviations

LV	Left ventricle
RV	Right ventricle
EF	Ejection fraction
EDV	End-diastolic volume
ESV	End-systolic volume
¹⁸ F-FDG	¹⁸ F-fluorodeoxyglucose
TAC	Time-activity curve

See related editorial, pp. 1958–1961

INTRODUCTION

Heart disease is frequently preceded by metabolic remodeling of the myocardium characterized by a switch from fatty acid metabolism to increased reliance on glucose utilization.^{1–9} In early stages of heart failure, systolic function may be preserved despite fundamental metabolic changes. Indeed, in the setting of systemic and pulmonary hypertension there is an association between increased left ventricular (LV) and right ventricular (RV) glucose metabolism and reduced LV and RV contractile function, respectively.^{9,10} Hence, the glucose analog ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) offers an opportunity for assessment of glucose metabolism using positron emission tomography (PET) in the setting of heart disease. ¹⁸F-FDG is an advantageous radiotracer as it is (1) considered an irreversible substrate, since it is trapped in the early metabolic pathway (after phosphorylation) and (2) ¹⁸F-FDG is a universal and low-cost agent for studies in cardiac metabolism.

Currently, cardiac imaging studies use a bolus injection of ¹⁸F-FDG in order to determine glucose utilization.^{3,10,11} With a bolus application, the uptake of the radiotracer is relatively stable after 30 minutes, enabling basic methods such as standard uptake values (SUV) to be used in assessment of baseline glucose metabolism. This currently used method has several potential confounds. First, glucose metabolism may not be at equilibrium over the course of a full experiment. Second, sequential measurements often made days or weeks apart introduce uncontrolled variables.¹² Additionally, there may be substantial intrasubject variability between repeated scans, as recently identified by differentiation of task- or stress-dependent changes from baseline glucose metabolism in the brain using two separate PET scans.^{13,14} Recently, a novel technique utilizing a continuous infusion of ¹⁸F-FDG has been proposed to study cerebral glucose metabolism.^{12,15} This technique uses a constant supply of ¹⁸F-FDG during the entire scan, which enables the dynamic assessment of task-specific changes in glucose metabolism, and a similar methodology is applied herein.

In most clinical scenarios, cardiac metabolism and function are not assessed simultaneously. While existing clinical imaging modalities provide exquisite measures of cardiac function, most cardiac disease states cannot be fully captured by measuring function alone. Furthermore, previous studies performed in human subjects have performed no simultaneous acquisition of measures of cardiac metabolism and contractile function, and cardiac parameters are measured under resting conditions.^{3,10} The induction of a physiological stressor, such as hypoxia or exercise, may elicit subclinical changes in cardiac function which are not typically observed under resting imaging conditions.^{16,17} Finally, to determine their relationship, cardiac metabolism and contractile function must be imaged together, which requires the use of simultaneous PET and MR imaging. Therefore, the purpose of this study was to develop a novel methodology using cardiac PET/MR imaging to study the dynamic relationship between contractile function and metabolism using a rest-stress scenario in a preclinical model.

METHODS

Animal Preparation and Study Design

Domestic pigs 45–50 kg (n = 10, female = 5) were obtained from the Swine Research Training Center (SRTC) at UW-Madison. Following an overnight fast, the animals were anesthetized using telazol (5 mg/kg)/xylazine (1 mg/kg IM). An endotracheal tube was inserted and a mechanical ventilator connected to 21% O₂, and maintenance anesthesia was maintained with 2% isoflurane for the PET/MR imaging study. ¹⁸F-FDG in saline solution was administered intravenously at a constant rate of 0.01 mL/s for 60 minutes for an injected dose of ~ 3.48 MBq/kg/h using a syringe pump (Medrad Spectra Solaris, Bayer Healthcare LLC, Whippany, NJ) with initial activity = ~ 5 mCi, as performed previously in cerebral imaging.¹² For assessment of plasma glucose and lactate, arterial blood samples were collected prior to the PET scan and approximately every 10 minutes (in between MR imaging sequences) after the start of ¹⁸F-FDG infusion from a seven French catheter inserted into the carotid artery. After 25–30 minutes of normoxic breathing (F_IO₂ = .209), hypoxic stress was induced by administering hypoxic air (F_IO₂ = .12). After approximately 10 minutes of settling time to equilibrate to a steady-state hypoxic response, 25–30 minutes of continued imaging was performed as shown in Figure 1. Throughout the imaging protocol, arterial oxygen saturation was assessed with pulse oximetry and blood pressure was monitored every two minutes with a sphygmomanometer. At the end of the imaging study, animals were euthanized by intravenous injection of Euthasol® (.22 mL/kg sodium pentobarbital + sodium phenytoin). Animal housing and handling was carried out under the guidelines of the Institutional Animal Care and Use Committees and conducted in pathogen-free facilities that are

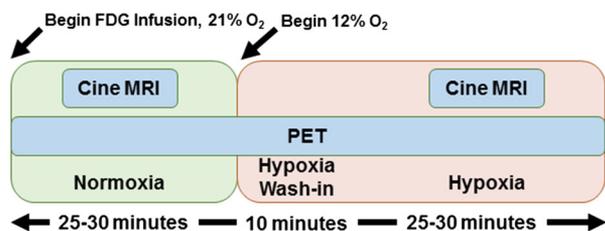


Figure 1. Study schema demonstrating the administration of hypoxic stress with dynamic PET/MR imaging.

accredited by the American Association of Accreditation of Laboratory Animal Care.

Simultaneous Cardiac PET/MR Imaging

Dynamic, simultaneous cardiac PET/MR imaging was performed on an integrated 3T scanner (Signa PET/MR, GE Healthcare, Waukesha, WI). MRI measures consisted of cardiac-gated tagged and untagged short-axis cine MR during breath holds with the following parameters: 35 cm FOV, 1.3 ms TE, 3.6 ms TR, matrix 224 × 224, slice thickness 7 cm, covering the entire LV. PET data were acquired simultaneously with MRI. Reconstruction parameters for dynamic PET are as follows: 60-second frame duration, 45 cm FOV, matrix 192 × 192, 28 subsets, 2 iterations, VPFX-S, time-of-flight, and 5 mm smoothing. Short-axis cine MR images were analyzed in software Segment version 2.0 (<http://segment.heiberg.se>) to determine LV and RV volumes. Dynamic PET data were analyzed in custom MATLAB (The Mathworks, Natick, MA) software. Three-dimensional regions of interest (ROIs) were manually drawn over the left ventricle plus septum (myocardial), in the triceps muscle (skeletal muscle), and blood pool (BP) utilizing the PET imaging comprising the temporal average of all dynamic activity. Example ROIs are shown in Figure 5. The ROIs were eroded by two cycles in order to control for partial volume

effects. The average value from each ROI was extracted for each time point to extract time-activity curves. The time-activity curves of the myocardial and skeletal muscle ROIs were normalized by the time-activity curve of the blood pool, to assess relative FDG uptake in active (myocardial) and passive (skeletal) muscle ROIs, which yields a near-linear time-activity ratio function. The slope of the time-activity ratio (myocardium:BP and skeletal muscle:BP) was calculated for the normoxic and hypoxic time periods separately. Patlak analysis^{15,18} to measure the net uptake rate (K_i) of ¹⁸F-FDG was performed using a home-built script written in MATLAB (The Mathworks Inc., Natick, MA) utilizing non-linear least squares fitting (lsqcurvefit). Myocardial glucose utilization rate was not calculated due to the known variability in the lumped constant during different metabolic states,¹⁹ which we believe would directly conflict with the rest-stress scenario used herein.

LV Strain Analysis

Three slices from the LV (apex, mid, and base) tagged short-axis cine MR images were used to analyze circumferential and radial dimensions (mean peak strain, systolic and diastolic strain rate, peak rotation, and peak torsion) using Segment strain analysis module (<http://segment.heiberg.se>). Peak rotation is quantified by mean angular distance by all of the tracking points around an axis of rotation, which is centered on mid-LV septum. Peak rotation is then defined by the difference in mean angular rotation in degrees between the apex and base. Peak torsion is calculated from the rotational difference of the heart for the most basal and apical slice chosen. The rotational difference is then normalized with the mean radius divided by the distance in the long axis.

Statistical Analysis

A paired *t* test was used to determine differences between normoxia and hypoxia exposure for cardiovascular

Table 1. Cardiovascular hemodynamic changes from normoxia to hypoxia (n = 10)

	Normoxia (21% O ₂)	Hypoxia (12% O ₂)	% Change	P value
Heart rate (beats/min)	97 ± 3	112 ± 4	14.7 ± 2.9	0.0005
Cardiac output (ml/min)	3228 ± 145	3931 ± 288	21.0 ± 5.9	0.0060
LV EDV (mL)	61 ± 3	54 ± 3	- 11.1 ± 3.1	0.0027
LV ESV (mL)	27 ± 2	18 ± 2	- 30.2 ± 6.9	0.0006
LV SV (mL)	33 ± 1	35 ± 2	5.7 ± 3.3	0.1065
LV EF (%)	56 ± 1	66 ± 2	9.0 ± 4.2	0.0016
SBP (mmHg)	113 ± 5	111 ± 6	- 1.3 ± 2.7	0.6400
DBP (mmHg)	41 ± 2	40 ± 2	- 3.2 ± 5.2	0.4690
MAP (mmHg)	65 ± 3	63 ± 3	- 2.9 ± 3.6	0.4138
Rate pressure product (mmHg × bpm)	10767 ± 740	12759 ± 1138	18.3 ± 6.3	0.0233
SpO ₂	99 ± 0.2	71 ± 1.7	- 27.8 ± 1.7	0.0001

Values represent Mean ± SEM

hemodynamics. Wilcoxon matched pairs signed rank test was used to determine differences in myocardial strain and kinetic PET assessments between normoxia and hypoxia. A linear regression was used to determine the relationship between LV EF and LV peak torsion. Repeated measures one-way ANOVA was used to determine differences in arterial plasma glucose and lactate changes over time (GraphPad Prism 6; GraphPad Software Inc., San Diego, CA). A *P* value < 0.05 was considered significant.

RESULTS

Hemodynamic Changes from Normoxia to Hypoxia

Transition from normoxia to hypoxia was associated with a decrease in arterial saturation from 99% to 71%. In response, there was an increase in heart rate (HR) (97 ± 3 vs 112 ± 4 beats/min), which in turn

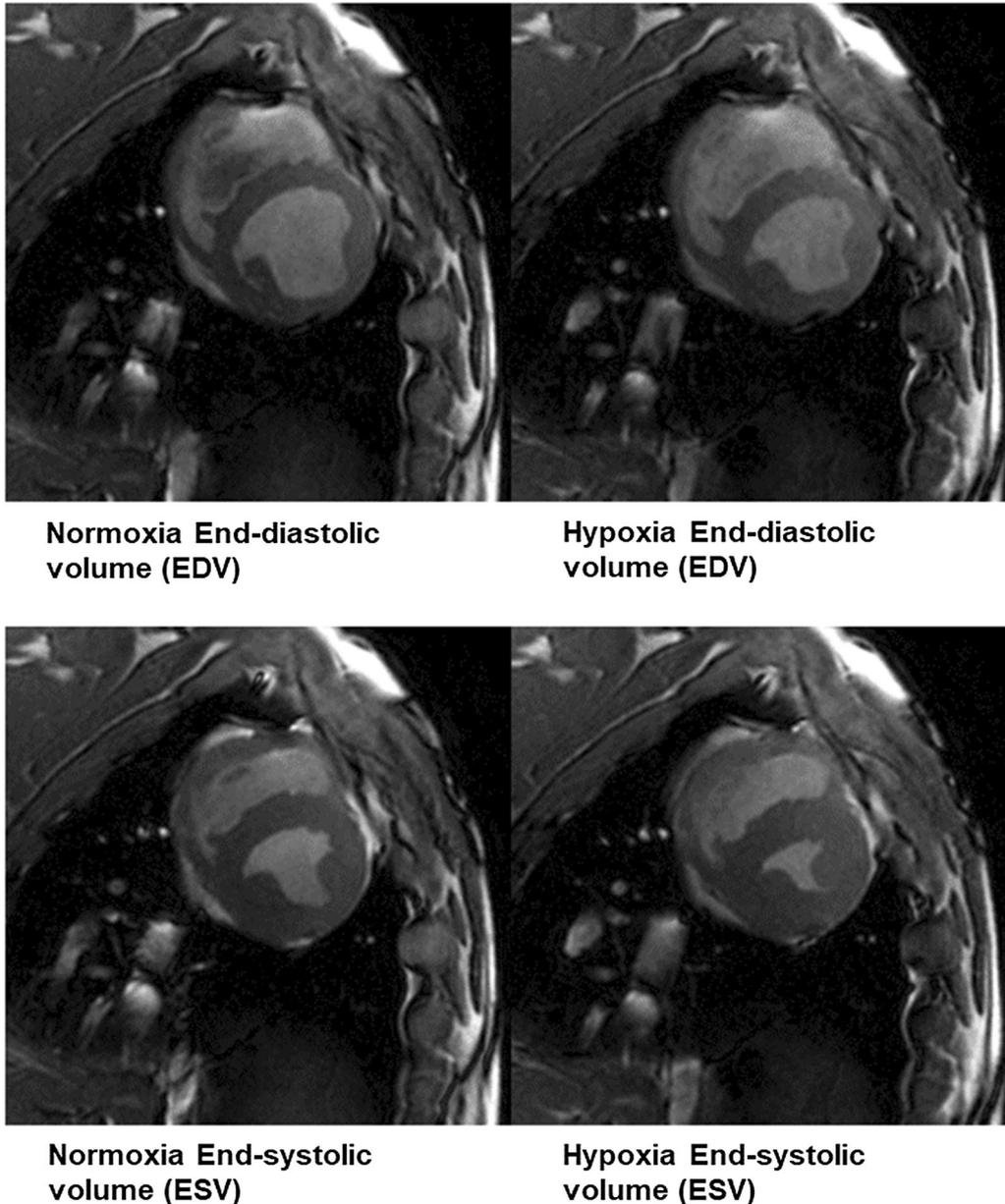


Figure 2. Example cine MR imaging at end diastole (top) and end systole (bottom). During hypoxia, there was a decline in both the end-diastolic volume (EDV) and end-systolic volume (ESV). ESV declined to a greater extent than did EDV.

resulted in an increased cardiac output (CO) (3228 ± 145 vs 3931 ± 288 mL/min), LV ejection fraction (EF) (56 ± 1 vs 66 ± 2), and rate pressure product (RPP) (10767 ± 740 vs 12759 ± 1138 mmHg \times beats/min), respectively (Table 1; $P < 0.05$ for all). There was no change in LV stroke volume. In addition, end-diastolic volume (EDV) (61 ± 3 vs 54 ± 3 mL) and end-systolic volume (ESV) (27 ± 2 vs 18 ± 2 mL) decreased from normoxia to hypoxia, respectively (Figure 2) (Table 1).

LV Strain in Response to Hypoxia

There were no differences in LV circumferential or radial strain (mean peak, systolic or diastolic strain rate) between normoxia and hypoxia. However, there was a significant difference in peak rotation and peak torsion in the LV during hypoxia as compared to normoxia ($P < 0.05$) (Table 2). Figure 3 is a representative image

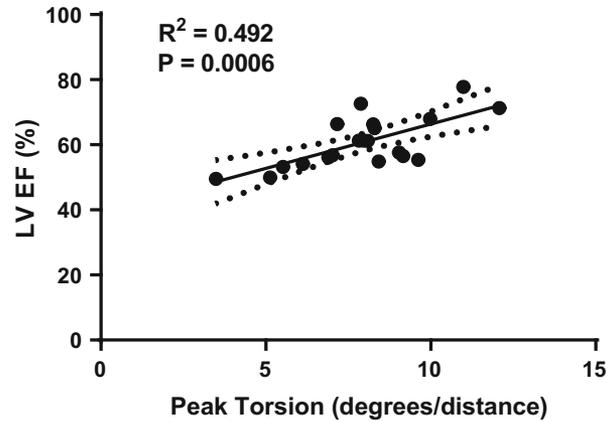


Figure 4. Relationship between LV EF and peak torsion.

of the tracking points and the axis of rotation that was used to determine LV strain with a representation of the circumferential and radial strain curves from the strain

Table 2. Left ventricular strain parameters in normoxia and hypoxia (n = 10)

	Normoxia (21% O ₂)	Hypoxia (12% O ₂)	% Change	<i>P</i> value
Mean peak circumferential strain (%)	- 12.66 \pm 0.43	- 12.82 \pm 0.32	1.77 \pm 2.43	0.8457
Circumferential systolic strain rate (%/s)	- 62.74 \pm 2.27	- 59.26 \pm 2.13	- 4.92 \pm 3.53	0.2324
Circumferential diastolic strain rate (%/s)	82.91 \pm 3.13	78.61 \pm 4.78	- 5.50 \pm 3.71	0.2754
Mean peak radial strain (%)	10.73 \pm 0.81	11.60 \pm 0.71	12.43 \pm 9.66	0.2754
Radial systolic strain rate (%/s)	52.80 \pm 3.36	55.76 \pm 4.21	10.17 \pm 11.54	0.5566
Radial diastolic strain rate (%/s)	- 52.44 \pm 3.56	- 45.60 \pm 5.51	- 8.31 \pm 14.04	0.4316
Peak rotation (degrees)	4.62 \pm 0.44	6.06 \pm 0.41	42.34 \pm 19.24	0.0059
Peak torsion (degrees/distance)	7.10 \pm 0.60	8.79 \pm 0.57	34.06 \pm 18.13	0.0371

Values represent Mean \pm SEM

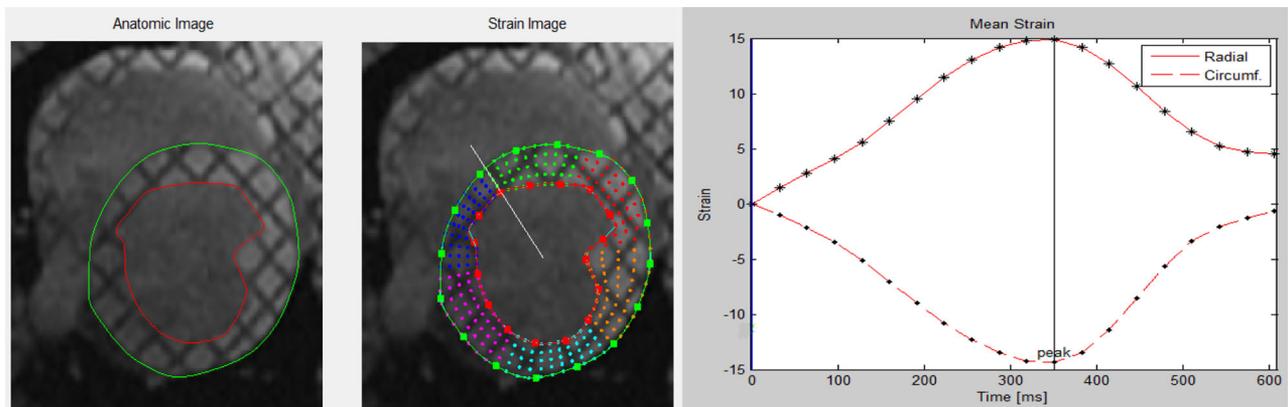
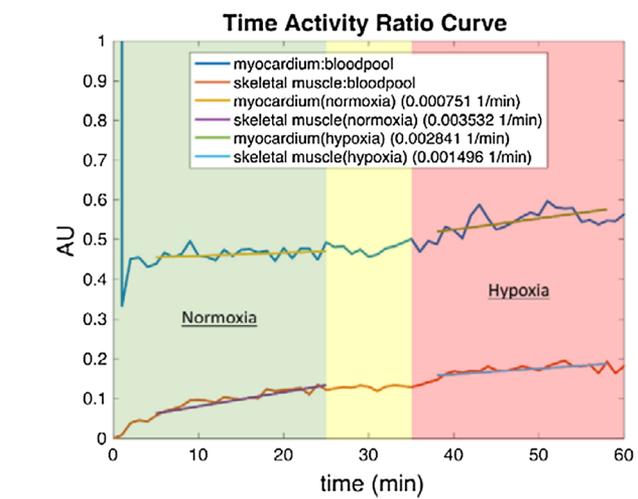
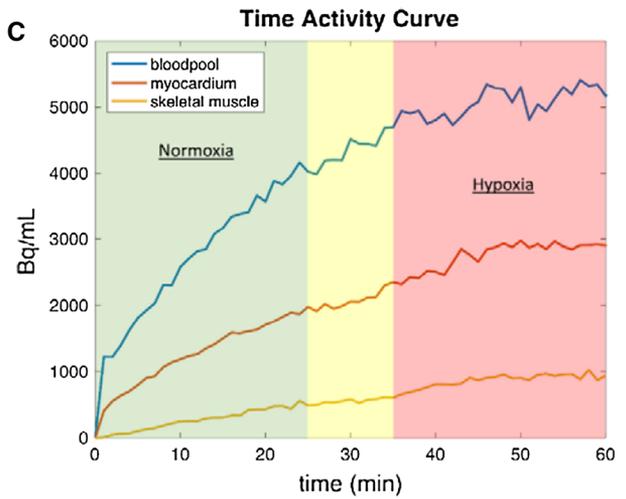
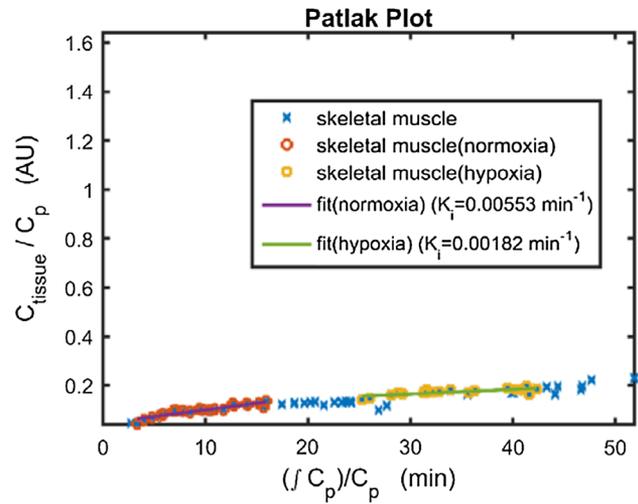
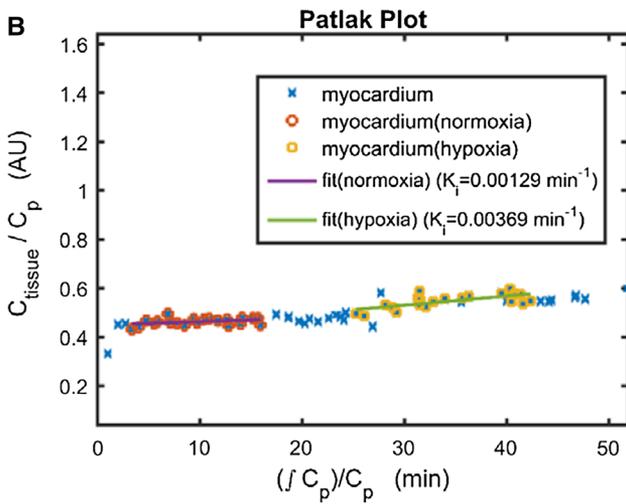
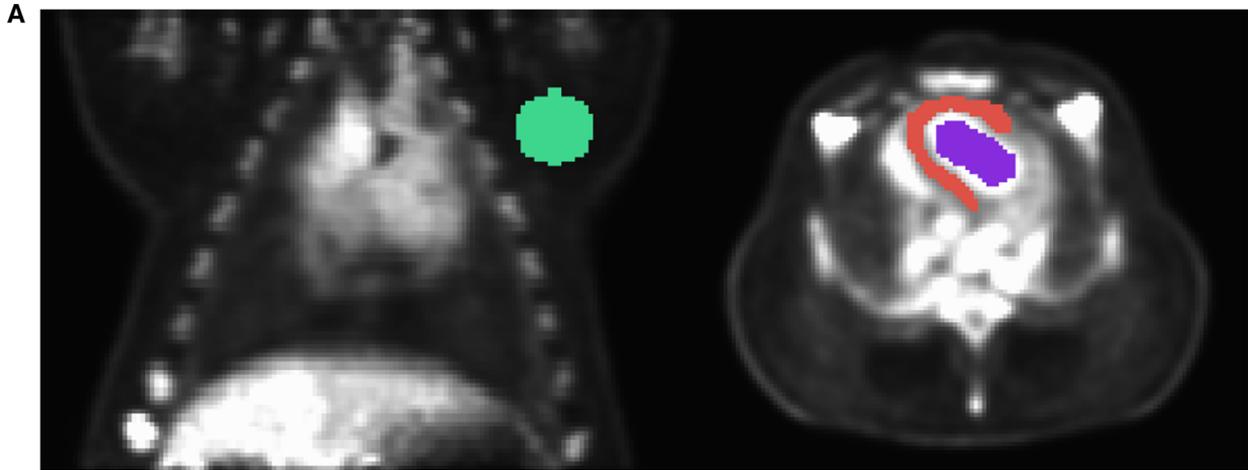


Figure 3. Representative image of LV strain analysis from tagged short-axis cine images (left) and circumferential and radial strain curves (right).



◀**Figure 5.** **A** Representative images of the ROIs drawn for the skeletal muscle (green), myocardium (red), and blood pool (blue). **B** Patlak plots for the myocardium (left) and skeletal muscle (right) during the rest-stress protocol. These plots show an increase in the K_i (myocardium) and a decrease in the K_i (skeletal muscle) during hypoxia. **C** Example of time-activity curve during ^{18}F -FDG infusion showing time-activity in the left ventricular blood pool, left ventricle (myocardium), and skeletal muscle (left). Example of time-activity ratio curve (obtained by normalization to the blood pool time-activity curve) for myocardium and skeletal muscle (right). The slope of the myocardium time-activity ratio during hypoxia is increased relative to normoxia and to skeletal muscle. The green background reflects time in normoxic breathing, the red background reflects time in hypoxic breathing, and the yellow background reflects time spent waiting for the hypoxic steady state (i.e., hypoxic gas administration began at 25 minutes).

analysis. Additionally, we determined that peak torsion is significantly associated with LV EF (Figure 4).

Changes in Glucose Metabolism

The respective ROIs drawn to determine the time-activity curves for skeletal muscle, myocardium, and blood pool are shown in Figure 5A. Representative Patlak plots for the myocardium and skeletal muscle (Figure 5B), and the slopes of the time-activity curve (TAC) were determined in normoxia and hypoxia (Figure 5C). Myocardial net uptake rate (K_i) increased during hypoxia, whereas glucose uptake rate decreased in resting skeletal muscle during hypoxia ($P < .05$) (Table 3/Figure 6). The TAC ratio slope curve, defined as the ratio of the myocardial to BP slope of the PET data, increased twofold ($P < .05$), suggesting increased LV glucose utilization as a result of hypoxic stress as shown in Table 3/Figure 6. Additionally, there was a significant decline in the skeletal muscle to BP slope in hypoxia (Table 3/Figure 6).

Arterial Plasma Glucose and Lactate Changes

There was a significant increase in arterial plasma lactate values during hypoxia as compared to normoxia ($P < .05$). There were no differences in arterial plasma glucose throughout the study duration (Figure 7), which supports the use of an image-derived input function for the Patlak modeling.

DISCUSSION

The purpose of this study was to establish the feasibility of performing a serial rest-stress scenario using PET/MR to simultaneously image cardiac glucose metabolism (as measured by ^{18}F -FDG) and cardiac function in response to increased myocardial workload, using hypoxic gas ($F_{\text{I}}\text{O}_2 = 0.12$) as a physiological stressor. We focused on changes in left ventricular function in hypoxia due to previous work demonstrating increased myocardial workload (i.e., increased heart rate and systolic function) in the LV during hypoxia.²⁰ When going from normoxia to hypoxia, there was a reduction in preload (LVEDV) combined with no change in afterload (MAP), suggestive of increased LV contractility. This was manifested as a 19% increase in LV EF coupled with a significant increase in ^{18}F -FDG uptake by the LV using both quantitative (K_i) and non-quantitative (myocardial/blood pool slope ratio) analysis during continuous ^{18}F -FDG infusion. Additionally, we saw a significant reduction in the slope of the blood pool TAC during hypoxia, which suggests a systemic increase in glucose utilization, an expected response to hypoxia. The rise in arterial lactate concentration during hypoxia demonstrates a global increase in anaerobic glucose metabolism. These results demonstrate the capability of using simultaneous cardiac PET/MR to measure meaningful changes in cardiac function and metabolism with a rest-stress scenario within the same

Table 3. Myocardial and skeletal muscle glucose utilization rate as measured by the two-compartment Patlak model

	Normoxia (21% O ₂)	Hypoxia (12% O ₂)	% Change	P value
Myocardial K_i	0.0031 ± 0.0010	0.0047 ± 0.0008	167 ± 58	0.0098
Skeletal muscle K_i	0.0038 ± 0.0004	0.0016 ± 0.0002	- 47 ± 16	0.0059
Blood pool (Bq/cc/min)	96.89 ± 15.22	21.18 ± 7.57	- 78 ± 13	0.0098
Myocardium: blood pool	0.0017 ± 0.0007	0.0033 ± 0.0007	261 ± 124	0.0020
Skeletal Muscle: blood pool	0.0026 ± 0.0003	0.0014 ± 0.0002	- 23 ± 27	0.0195

Slope of time-activity curves in the myocardium and skeletal muscle normalized to the blood pool slope in normoxia and hypoxia (n = 10). Values represent Mean ± SEM

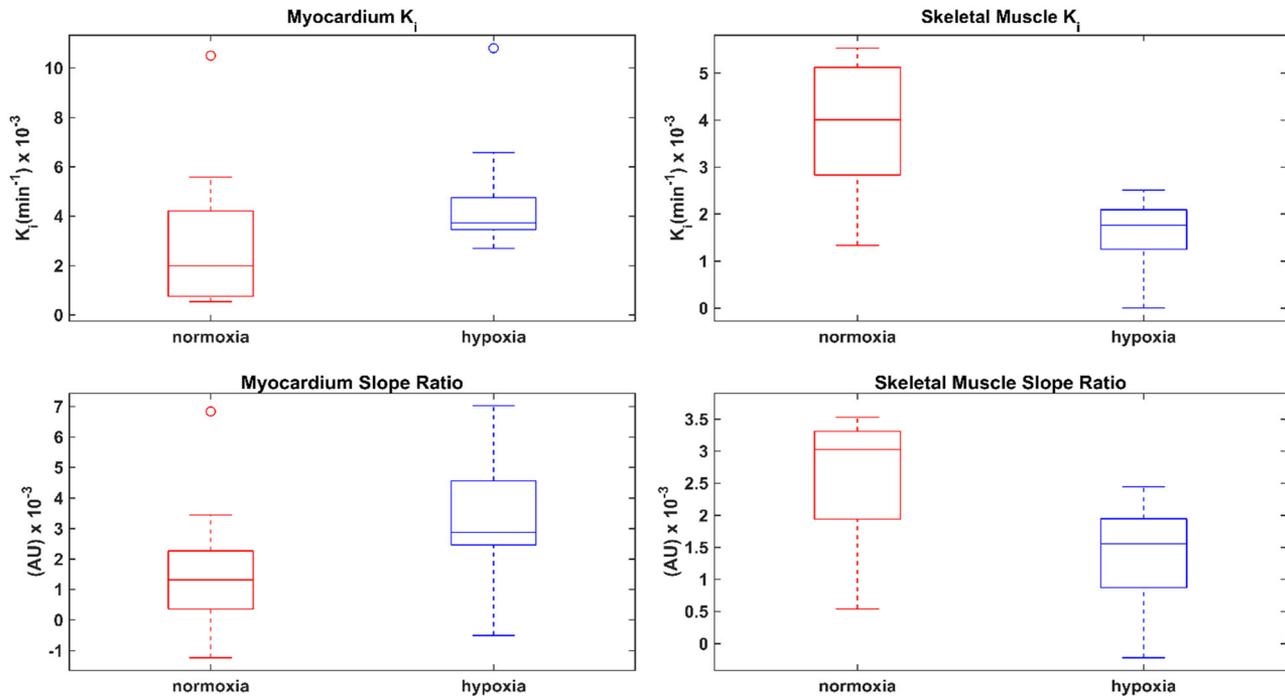


Figure 6. Box plots represent the median (central mark) and the edges of the box are the 25 and 75%, the whiskers extend to the most extreme data points not considered outliers, and outliers (open circles) are plotted individually in normoxia (red) and hypoxia (blue). Patlak rate constant (K_i) (top row) shows a significant hypoxic-dependent increase in the myocardial uptake rate and a decrease in the skeletal muscle uptake rate. Box plots show changes that are similar in magnitude and direction as determined by the Patlak rate constant (K_i) during hypoxia in the myocardium: blood pool and skeletal muscle: blood pool slope ratios (bottom row). Refer to Table 3 for relevant P values for K_i and slope ratio.

scanning protocol, which may have many potential applications clinically.

We chose to use acute hypoxia as a stressor in this proof-of-concept study utilizing this serial rest-stress technique combined with continuous infusion because of the well-known cardiac hemodynamic effects^{16,20–23} and augmentation of myocardial glucose uptake²⁴ induced by acute hypoxia. Acute hypoxia increases heart rate, cardiac output, and LV systolic function, all of which increase myocardial workload,^{16,20–23} which corroborates our findings.

Cardiac magnetic resonance tissue tagging permits intramyocardial displacement and strain to be measured non-invasively by examining the motion of identifiable points distributed throughout the myocardium.^{25–27} We found that LV EF increased in response to hypoxia; however, circumferential or radial strain parameters remained unchanged. Notably, we saw a significant increase in peak rotation and torsion in the LV in response to hypoxic stress compared to normoxic resting conditions. Myocardial torsion is a fundamental component of LV function.²⁸ Torsion is produced due to the

double helical nature of myocardial fibers, which results in systolic rotation in opposite directions between the apex and base of the left ventricle in the longitudinal axis.^{29–31} Although we did not observe an increase in LV strain in the circumferential or radial axis, LV torsion has been determined to be correlated with LV longitudinal strain.³² The increased LV EF in hypoxic conditions is significantly associated with an increase in LV peak torsion and possibly an increase in long-axis strain, although we did not perform long-axis strain analysis.

Previous works in ex vivo models using increased afterload or catecholamines to increase myocardial workload have demonstrated increased glucose utilization.^{33,34} Increases in LV contractility, HR, CO, and rate pressure product (RPP) with acute hypoxia in our study demonstrate an increased myocardial workload which was coupled to a significant augmentation of glucose uptake into the LV during hypoxia. This finding of increased glucose utilization in the heart in our study is similar to the findings in the human heart, although the previous study did not measure cardiac contractile

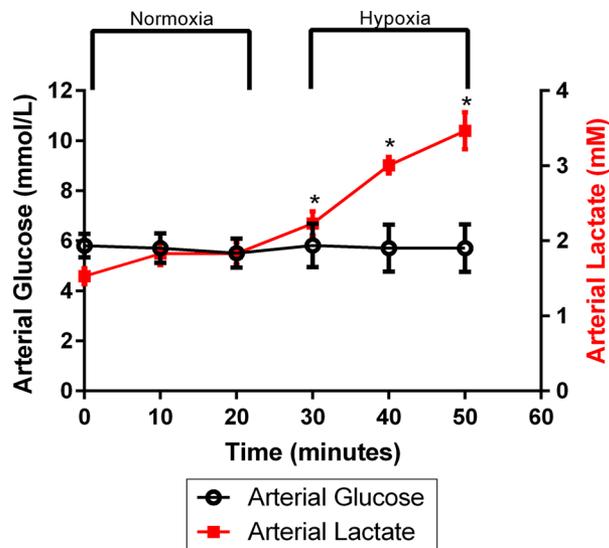


Figure 7. Plasma obtained from the carotid artery was used to determine changes in glucose and lactate during the rest-stress protocol. There were no differences in arterial plasma glucose over time, while hypoxia induced an increase in arterial plasma lactate. Values represent Mean \pm SEM. *indicates significant increases in arterial plasma lactate during hypoxic stress compared to resting conditions ($P < 0.05$).

function.²⁴ These findings are supported by a concomitant rise in arterial lactate during hypoxia, which suggests a global increase in anaerobic glycolysis. Further support of a systemic increase in glucose utilization was the finding of an approximate fourfold reduction in the slope of the blood pool TAC. We used resting skeletal muscle as a reference tissue and found that FDG uptake was reduced in hypoxia, whereas the myocardial FDG uptake was augmented in combination with increased myocardial work. Indeed, hypoxia and/or anoxia increases plasma membrane glucose transporters in cardiac muscle³⁵ which is an important adaptation to hypoxia due to restricted use of fatty acids at low oxygen levels.^{36,37}

We utilized a novel approach to dynamically measure glucose utilization in the heart by administering ^{18}F -FDG via a continuous infusion. One group has used the continuous infusion approach to measure dynamic changes in glucose uptake in the brain.¹² These investigators combined continuous infusion of ^{18}F -FDG with fMRI (PET/MR) at rest and used visual stimulation to acutely increase brain workload/activity. They were able to dynamically measure increased glucose utilization with ^{18}F -FDG during intermittent visual stimuli as compared to resting conditions.¹² Similarly, we were able to demonstrate increased ^{18}F -FDG uptake into the myocardium during hypoxia-induced increased myocardial workload. The only previous study to determine the

effects of hypoxic stress on ^{18}F -FDG uptake in the heart during hypoxia used a bolus injection method and randomized human subjects into a normoxia or hypoxia group instead of scanning each subject under both conditions.²⁴ Continuous infusion of ^{18}F -FDG enables a rest-stress scenario during a single dynamic imaging study.

One major advantage to our approach of continuous infusion is that we performed a rest-stress protocol in each animal with the use of ~ 5 mCi of radiotracer. Previous work that looked at rest and pharmacologic stress/cognitive task-dependent changes in cerebral glucose metabolism used two separate PET scans which required a greater amount of radioactivity, in addition to increased intrasubject variability.¹⁴ Our study establishes the feasibility using continuous infusion of ^{18}F -FDG and PET/MR to determine cardiac glucose utilization and functional changes during normoxia rest and hypoxic stress in a single imaging session, which is a fundamental improvement over the standard bolus injection technique which may mitigate known intrasubject variability if rest and stress procedures are performed at different times rather than serially.

Furthermore, demonstrations of quantitative kinetic analysis using general linear model (GLM) approaches to Patlak using infused PET radiotracers have been previously reported,¹⁵ and these quantitative imaging outcomes, as used herein, could be used to assess cardiac disease. In addition to using the quantitative kinetic approach with Patlak analysis, we also utilized a semi-quantitative approach to determining myocardial glucose uptake during rest and stress. The advantage of the semi-quantitative approach (slope ratio) used here is that it could be used in an environment that does not require the use of arterial sampling to estimate plasma ^{18}F -FDG activity. We found that the K_i values were of the same order of magnitude and of similar values as the slope ratio presented in this study, suggesting that this semi-quantitative approach may be a quick and practical means of determining metabolic changes in a clinical setting.

Until now, there have been very few studies using cardiac PET/MR and all of these studies have performed assessments of cardiac function and metabolism under resting conditions. However, in most cardiac conditions, cardiac dysfunction is best elicited with the use of stress, such as exercise.^{38–40} Therefore, we used the strength of PET/MR to develop a cardiac PET/MR stress test that may translate to studying human populations of cardiac disease. To our knowledge this was the first study to demonstrate significant changes in cardiac function and glucose utilization during a rest-stress scenario by combining dynamic imaging of cardiac function and glucose metabolism during a single scanning session.

Future use of an MRI compatible exercise ergometers⁴¹ during cardiac PET/MR scans may enable investigators and clinicians to unmask cardiometabolic and functional sequelae prior to clinical symptoms of disease or to assess prognosis of a disease state. Indeed, one study has used static PET acquisition to demonstrate increased ¹⁸F-FDG uptake into the myocardium with exercise.⁴² One of the strengths of cardiac PET/MR is that it permits reconstruction of accurate fusion images to simultaneously study the tight coupling between metabolism and contractile function in the heart. Studies using a cardiac PET/MR stress test, similar to the approach herein, would permit investigators to obtain simultaneous measurements of cardiac (change in contractile function during stress) and metabolic reserve (change in substrate metabolism from rest to exercise) in order to more directly examine the relationship between cardiac contractile function and substrate metabolism. Previous work in a preclinical model of heart failure has demonstrated that increased reliance on glucose (i.e., glycolysis) was associated with reductions in contractile function at rest, yet at higher cardiac workloads the failing heart did not demonstrate further increases in glucose utilization as compared to control hearts suggesting a reduction in glucose metabolic reserve.³³ These measures of cardiac substrate metabolism and contractile function during stress would permit a better understanding of the link between cardiac energetics and function in health and disease. For example, little is known about the progression of metabolic abnormalities throughout the stages of left or right heart failure and the use of a cardiac PET/MR stress test during early stages of heart failure would provide clinicians with a better understanding of pathological progression and may offer more prognostic value.

LIMITATIONS

This pilot study has demonstrated the feasibility of a rest-stress PET/MR imaging protocol to determine metabolic and functional changes in the myocardium, yet questions remain. For instance, this study was performed in anesthetized swine, and there is need to determine the feasibility of using a rest-stress scenario in human subjects. We assessed the slope of a time-activity ratio function and the Patlak rate constant during the assumption of a metabolic steady state during rest and stress, which we acknowledge has potential limitations. For instance, as hypoxia exposure increased with time, we saw further increases in arterial lactate concentration which suggests further changes in whole body metabolism. This suggests that although S_pO_2 was relatively constant after 10 minutes of hypoxia wash-in, cardiac glucose metabolism may not have been at steady state

after extended hypoxia exposure. It is therefore possible that ¹⁸F-FDG uptake by the heart was underestimated, especially in the final minutes of hypoxia exposure. Therefore, future work to measure dynamic changes of ¹⁸F-FDG within the stress condition (e.g., early vs late stress) could address this potential limitation.

Another limitation is that we did not measure coronary flow/perfusion. Since we applied a stress, it is likely that coronary perfusion changes occurred, especially when cardiac workload increased during hypoxia. A previous study determined the effect of enhanced coronary perfusion on ¹⁸F-FDG uptake into the myocardium and found that increasing coronary flow with nitroprusside resulted in no changes in glucose uptake.^{43,44} These results demonstrate that increasing flow without increasing myocardial workload does not result in an increase in metabolic fuel uptake. This is similar to a finding that used hypercapnia to stimulate cerebral blood flow and found that increased flow did not alter ¹⁸F-FDG uptake rate into the brain.¹² Given our application of steady-state rest and stress conditions, we do not expect myocardial flow to change during each state, and thus it is unlikely that steady-state changes in flow would change the slope of the time-activity ratio functions. Additionally, arterial hypoxemia results in peripheral vasodilation and increased skeletal muscle blood flow^{45,46} which should further enhance ¹⁸F-FDG uptake into the skeletal muscle, yet there was a decrease in the skeletal muscle to blood pool slope during hypoxia exposure. Taken together, these findings demonstrate that glucose uptake in striated muscle is regulated by metabolic demand when blood flow is not a limiting factor.

NEW KNOWLEDGE GAINED

This study has demonstrated the feasibility of performing a cardiac PET/MR stress test which showed identifiable changes during simultaneous acquisition of cardiac metabolic and functional variables. This application has translational implications to the study of cardiac disease progression in human populations. Further development of this approach utilizing exercise as a physiological stressor in human subjects is warranted.

CONCLUSION

In conclusion, this was the first study to our knowledge to develop a novel cardiac PET/MR stress test to determine dynamic changes by simultaneous measures of cardiac contractile function and glucose metabolism. Further work refining the kinetic modeling of the radiotracer and workflow for PET/MR during rest-stress scenarios is still needed, but the application for

this novel non-invasive methodology has tremendous potential to elucidate mechanisms of human cardiac disease, in addition to the management of known disease states.

Acknowledgements

We would like to thank Dan Consigny, Sara John, Jenelle Fuller, and Kent MacLaughlin for their contributions to this study.

Disclosure

The authors have nothing to disclose.

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