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A Real-Time Magnetic Resonance Imaging Technique for Determining Left Ventricle Pressure-Volume Loops

Walter R.T. Witschey, PhD^{1,2}, Francisco Contijoch, MS^{1,2}, Jeremy R. McGarvey, MD^{1,2}, Victor A. Ferrari, MD⁴, Michael S. Hansen, PhD⁵, Madonna E. Lee, MD^{1,2}, Satoshi Takebayashi¹, Chikashi Aoki¹, Julio A. Chirinos, MD³, Paul A. Yushkevich, PhD³, Joseph H. Gorman III, MD^{1,2}, James J. Pilla, PhD^{1,3}, and Robert C. Gorman, MD^{1,2}

¹Gorman Cardiovascular Research Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

²Department of Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

³Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

⁴Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

⁵National Institutes of Health, Bethesda, MD

Abstract

Background—Rapid determination of the left ventricular (LV) pressure-volume (PV) relationship as loading conditions are varied is the gold standard for assessment of LV function. Cine magnetic resonance imaging (MRI) does not have sufficient spatiotemporal resolution to assess beat-to-beat changes of the LV PV relationship required to measure the LV end-systolic elastance (E_{ES}) or preload-recrutable stroke work (PRSW). Our aim was to investigate real-time MRI and semi-automated LV measurement of LV volume to measure PV relations in large animals under normal and inotropically stressed physiologic conditions.

Methods and Results—We determined that PV relationships could be accurately measured using an image exposure time $T_{ex} < 100$ ms and frame rate $T_{fr} < 50$ ms at elevated heart rates (~140 bpm) using a golden angle radial MRI k-space trajectory and active contour segmentation. With an optimized exposure time ($T_{ex} = 95$ ms and frame rate $T_{fr} = 2.8$ ms), we found that there was no significant difference between cine and real-time MRI at rest in end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), stroke volume (SV) or cardiac output (CO) ($n=5$, $P<0.05$) at either normal or elevated heart rates. We found E_{ES} increased from $1.9 \pm$

Corresponding Author: Robert C. Gorman, M.D., Gorman Cardiovascular Research Group, Perelman School of Medicine, University of Pennsylvania, Smilow Center for Translational Research, 3400 Civic Center Blvd, Philadelphia, PA 19104-5156, 215-746-4087, robert.gorman@uphs.upenn.edu.

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0.7 to 3.1 ± 0.3 mmHg/mL and PRSW increased from 6.2 ± 1.2 to 9.1 ± 0.9 mmHg during continuous IV dobutamine infusion ($n=5$, $P<0.05$).

Conclusions—Real-time MRI can assess LV volumes, E_{ES} and PRSW at baseline and elevated inotropic states.

Introduction

Left ventricular (LV) performance is coupled to loading conditions (i.e. preload and afterload) and myocardial contractility [1, 2]. Therefore, load-independence is an important means to isolate and study LV contractility in preclinical studies of cardiovascular pharmaceuticals and devices [3]. Pioneering work by Sagawa, et al. and Glower et al. demonstrated the validity of end-systolic elastance (E_{ES}) and preload recruitable stroke work (PRSW) as load-independent measures of myocardial contractility [4, 5]. Both E_{ES} and PRSW are dependent on the simultaneous measurement of LV pressure and volume as loading conditions are rapidly varied. Precise and rapid assessment of LV pressure is readily achieved with high fidelity catheter-based pressure transducers; however, such measurements of LV volume are much more difficult and less reliable.

The most commonly used technologies for measuring LV volumes are ultrasonic sonomicrometry transducers and conductance catheters. Sonomicrometry employs small ultrasonic transducers that transmit sound signals to each other; the distance between transducers is determined by the transit-time of the signals. This technique is limited by the requirement for surgical implantation and assumptions related to LV shape and wall thickness. Conductance catheters measure electrical conductance of LV blood, which is then converted to blood volume using formulae that are dependent on the electrical resistance of blood, distance between electrodes, parallel resistance of the myocardium and poorly defined constants. Most of these parameters are difficult to measure accurately and vary over time and between subjects.

Cardiovascular magnetic resonance allows for excellent tomographic imaging of the LV [6–9]; however, slow acquisition times prohibit continuous estimation of LV volume and transient volume changes during preload reduction. Echo planar imaging MRI allows for a significant reduction in scan time [6, 10], but there would be clear advantages to using real-time MRI to continuously measure beat-to-beat changes in LV volume.

In this study, we developed a real-time MRI technique to continuously measure LV volume and pressure during transient loading conditions in anesthetized pigs. Calibration data is first acquired from a volumetric cine MRI scan and then a single short axis real-time scan is performed at mid-ventricle. The real-time approach used a non-Cartesian sampling trajectory, in which consecutive k-space projections are separated by the golden angle (~111 degrees). Since consecutive golden angle projections are uniformly distributed in k-space, we were able to retrospectively reconstruct images from any number of projections to determine the spatiotemporal resolution sufficient to measure LV PV loops and derive E_{ES} , PRSW, and other PV relationships.

Material and Methods

Overview

A schematic depicting the methodology used to determine real-time LV PV relationships from MRI is shown in fig. 1. This approach solves for real-time 3D LV volumes from a 2D single-slice scan at mid-ventricle, using a high-resolution 3D cine MRI scan to calibrate (scale) the real-time data. 3D cine MRI scans were acquired at each inotropic state (rest and stress) to minimize the calibration error. Time-varying LV volume was determined by semi-automated active contour segmentation of 3D cine data (fig. 1a). LV short axis images were reconstructed from undersampled 2D radial k-space data (fig. 1b and c) and MR radiofrequency pulses were synchronized with intraventricular pressure to match each image frame to measured pressure in real time (fig. 1d). The time-varying relationship between the 2D slice volume and total LV volume was determined during the cardiac cycle (fig. 1e) and used to calibrate real-time slice volumes; the result was a measurement of global LV PV relationships (fig. 1f).

Instrumentation

A physiologic monitoring system was used to synchronize LV pressure with the MRI acquisition. The fiber optic signal was converted to a 0–5 V electronic signal (O/E converter, Siemens Healthcare). LV pressure was obtained using a pressure transducer (Mikro-Tip; Millar Instruments, Houston, TX) and connected to a transducer amplifier (Gould). 0–5 V LV pressure and radiofrequency pulse timing were digitized at 2 kHz with a manifold analog to digital converter (NI USB6009 Multifunction DAQ, National Instruments, Austin, TX), and recorded (LabView; National Instruments, Austin, TX).

Animal Procedures

The University of Pennsylvania Institutional Animal Care and Use Committee approved all experiments. Healthy Yorkshire swine (N=5, mean weight = 44.3 ± 6.0 kg) were sedated with 25–30 mg/kg intramuscular ketamine, intubated and anesthesia was initiated and maintained with a mixture of isoflurane (2–5%) and oxygen throughout the procedure. Central arterial and venous access was surgically obtained in each animal. Transient LV preload reduction was achieved by expandable vascular occluders (In Vivo Metric; Healdsburg, CA) placed around the inferior (20 mm) and superior (24 mm) vena cavae. Occluding devices were inflated gradually over 20–30 seconds to transiently reduce LV volume.

MRI

MRI was performed on a 3 T clinical imaging system (Tim Trio Model, Siemens Healthcare, Erlangen, Germany). Cine CMR data was obtained using a 2D multislice retrospectively-gated cine balanced steady-state free-precession acquisition with the following imaging parameters, TE = 1.2 ms, TR = 2.4 ms, matrix = 192×156 , FOV = 300×240 mm², BW = 1184 Hz/pixel, segments = 7, temporal resolution ~ 20 ms, phases = 30, and 4 mm slice thickness.

Real time cine MRI data was obtained using a 2D radial k-space trajectory with golden angle view ordering [11] and the following imaging parameters, TE = 1.82 ms, TR = 2.8 ms, $N_p = 128$, FOV = 280×280 mm, BW = 1184 Hz/pixel.

Non-Cartesian Parallel Image Reconstruction

2D radial k-space data was reconstructed using a non-Cartesian SENSE [12], utilizing view sharing, a conjugate gradient solver [13]. Image reconstruction was performed on a graphical processing unit workstation using open source software [14].

Active Contour Segmentation of Cine and Real-Time MRI

One practical challenge was the time-efficient determination of LV volume from thousands of image frames. Manual segmentation of the endocardial contour was exceedingly burdensome because thousands of images from a single experiment require segmentation. To overcome this challenge, we used a semi-automatic active contour, level-set algorithm to segment real-time image frames and extract LV volume. Both cine and real-time LV volumes were measured using a semi-automatic segmentation algorithm. Segmentation was performed by active contours [15].

Calibration Scan

A full volume cine MRI was acquired under rest and stress conditions and used to calibrate (scale) single slice 2D real-time MR images obtained at mid-ventricle. The real-time LV volume was computed from a single slice using the slice-to-volume ratio determined by the calibration scan, using ES and ED as reference points for interpolation at each point in the cardiac cycle. ES was the time at maximum elastance ($= P/V_{\max}$) and ED was defined as the bottom right corner of the PV loop. We realized that the calibration approach would introduce error if there were differences in heart rate between the calibration and real-time scan, so we estimated the mean and peak percent difference (ϵ_m and ϵ_p) between these curves at normal and elevated heart rates (cf. fig. 1e). Stroke work was calculated by trapezoidal numerical integration. Mean end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), ejection fraction (EF) and stroke work (SW) were reported for 5–10 heartbeats at end-expiration at rest. The end-systolic pressure volume relationship (ESPVR) was estimated using a linear model. The volume axis intercept of the ESPVR V_0 was the x-intercept of the ESPVR. PRSW was determined by trapezoidal numerical integration.

Statistical Analysis

To examine differences between cine and real-time measured LV parameters, differences caused by inotropic state or the effect of preload reduction on hemodynamic function, we analyzed results using a paired-samples t-test at a significance level of $P < 0.05$ (SPSS Statistics, IBM, Version 20). Each pair of the paired-samples t-test was from the same animal.

Results

The Effect of Image Exposure Time and Frame Rate on Temporal Resolution and Measured LV Volume

We did not know *a priori* what temporal resolution was sufficient to measure PV relationships. To address this question, we varied two reconstruction parameters that affect temporal resolution, the image exposure time T_{ex} and image frame rate T_{fr} and measured LV volume and pressure. T_{ex} is analogous to camera shutter opening time, since it determines how much data is used to reconstruct a single image frame. $T_{ex} = N_p TR$, where N_p was the number of radial projections per image frame and TR the usual repetition time of the MRI pulse sequence. Image frame rate T_{fr} was the time between adjacent image frames in playback and was varied by sharing radial projections between image frames. The highest possible T_{fr} was achieved when $N_p - 1$ radial projections were shared between adjacent image frames, i.e. $T_{fr} = TR$. While observable motion, such as LV wall motion, may be reduced with increasing T_{ex} and T_{fr} , longer T_{ex} improved the image signal-to-noise ratio and facilitated more dense and uniform k-space sampling density, reducing radial streak artifacts.

We measured the relationship between T_{ex} and EDV, ESV, EF and PV loops from 12 consecutive heart beats during rest (mean heart rate = 111 ± 23.1 bpm, $n=1$) and during continuous infusion of dobutamine (mean heart rate = 140 ± 12.4 bpm, $n=1$) and in comparison to a breathhold, Cartesian, k-space segmented, retrospective cine acquisition ($T_{fr} = 22$ ms). We found that there was a reduction in measured EDV and increase in ESV with increasing T_{ex} (fig. 2a,b; fixed $T_{fr} = 2.8$ ms). Overall, LV volume changes were the most rapid at end-systole, resulting in significantly underestimated EF for $T_{ex} > 100$ ms. Therefore, suboptimal T_{ex} did not capture fast motion to measure LV volume at elevated heart rates.

Time-varying volumes for images reconstructed at $T_e = 72.8$, 162.4 and 560 ms are shown in fig. 2d. There was some variation in EDV due to respiratory motion, but overall we observed that accurate volumes could be measured even at intermediate exposure time ($T_{ex} = 162.4$ ms). The PV loop shape was progressively distorted as T_{ex} increased and this was a direct consequence of image blurring. (fig. 2e). Maximum loop distortion was observed at high T_{ex} , with overlap of diastolic and systolic isovolumic trajectories. Considerable blurring was observed at very low exposure time ($T_{ex}=560$ ms; fig. 2g) such that EDV and ESV were nearly the same value..

We next found the relationship between T_{fr} and LV function parameters (at fixed exposure time $T_{ex} = 95.2$ ms; $N_p = 34$). A relationship was observed between EDV, ESV, EF and T_{fr} , such that sufficiently low frame rate greatly reduced apparent LV EF (fig. 3). Overall, we observed that T_{fr} should be somewhat lower ($T_r < 50$ ms) than T_{ex} to correctly measure LV volume.

Comparison of Real-Time and Cine MRI PV Loops

We sought to determine whether real-time MRI could reproducibly measure PV relationships in agreement with cine MRI at baseline in several animals. We compared real-

time and cine PV loops, reconstructing real-time image frames at $T_{ex} = 95.2$ ms and $T_{fr} = 2.8$ ms based on our observations in fig. 2–3. Time-varying pressure and volume and PV loops are shown for one animal in fig. 4. As expected, a left- and upward shift in the PV loop under increased inotropic state was observed. Similar results were observed from PV loops in all animals. Average hemodynamic parameters under rest and stress conditions are shown in table 1. There was no significant difference between EDV, ESV, EF, SV or SW measured with cine and real-time at either normal or elevated heart rates ($P < 0.05$; $n=5$).

Although there was excellent agreement between baseline cine and real-time MRI at normal and elevated heart rates, determination of global LV volume from calibrated 2D real-time MRI could introduce errors if the heart rate changed between the calibration and real-time scans. To address this question, we found the error resulting from using calibration data obtained at resting heart rates to calibrate real time data at elevated heart rates. We estimated then the mean and peak error in ventricular volume (ϵ_m and ϵ_p) resulting from heart rate differences between rest (mean heart rate = 112 bpm) and stress (mean heart rate = 141 bpm) calibration scans. We found $\epsilon_m = 5.6\%$ and $\epsilon_p = 14.2\%$ ($n=5$, cf. fig. 1e) and, since the anesthetized animals did not greatly increase their heart rate in response to preload reduction, we believe these errors represent upper-limits to the true error. Since, for all other experiments, the calibration scan at each inotropic condition, measured LV volume was unaffected by heart rate changes between rest and stress studies.

Elastance at Rest and During Augmented Contractility

We then investigated E_{ES} , E_{ED} , and the volume at zero pressure V_0 by observing PV relations during transient LV volume reduction using real-time MRI (fig. 5). We observed that the slope of the ESPVR appeared to increase at low EDV, indicating nonlinearity and load-dependence, possibly a result of sympathetic response to preload reduction. Overall, E_{ES} increased from 1.9 ± 0.7 to 3.1 ± 0.3 mmHg/mL ($P < 0.05$; $n=5$). Residual volumes were not different from zero, suggesting that the normal LV efficiently eliminated blood ($V_{0,rest} = -0.1 \pm 6.5$ mL, $V_{0,stress} = 2.0 \pm 4.5$ mL, $P < 0.05$; $n=5$).

Preload-Recrutable Stroke Work

We investigated whether there was a decrease in stroke work (SW) under reduced loading conditions as expected by the Frank-Starling mechanism and if there was a response to inotropic state. Stroke work was measured continuously throughout the unloading period and during recovery following release using real-time MRI (fig. 6a,c). Not only was SW reduced under resting conditions ($SW = 221.3 \pm 51.9$ to 90 ± 31.8 mmHg mL, paired t-test, $P < 0.05$; $n = 5$), but also, in an augmented inotropic state, and for the same EDV, SW was increased as shown by the increased slope of the Frank-Starling curve (6.19 ± 1.2 to 9.1 ± 0.9 mmHg, $P < 0.05$; $n = 5$) (fig. 6b).

Comment

Recording LV pressure-volume data during rapidly changing loading conditions can yield important information regarding myocardial systolic performance. The validity of such analysis is highly dependent on an accurate and rapid measurement of LV volume and

pressure simultaneously. A number of techniques have been used to rapidly estimate LV volume; however, all require the use of major simplifying assumptions that limit accuracy. We developed a technique utilizing MRI to continuously measure LV volume and pressure simultaneously, allowing for the quantitative assessment of important load-independent measures of LV contractile function.

Image temporal resolution and measured LV volume were found to be dependent on image exposure time and frame rate; the upper limits for these parameters were established at an elevated heart rate ($T_{ex} < 100$ ms, $T_{fr} < 50$ ms). A new development was the use of a semi-automated active contour segmentation approach for determination of LV volume from thousands of image frames. Altogether, the strong agreement between real-time and cine MRI demonstrates that the real-time methods, combined with a suitable semi-automated segmentation, can be used to obtain accurate PV relations, even at elevated heart rates.

Besides the approach shown here, PV relationships can be also estimated from stroke volume using real-time 2D through-plane velocity encoded MRI at the ascending aorta [16]. We chose instead a 2D intraventricular approach because we plan to measure regional elasticity, which potentially could be obtained from 2D real-time MRI directly from observed wall motion or strain using computational motion tracking. Variations in regional myocardial elasticity in normal subjects, let alone patients with cardiovascular disease, are relatively unknown. A limitation of this approach is that regional wall motion abnormalities can result in inaccurate measurements of global PV relationships, depending on the position of the 2D real-time imaging slice. If the 2D slice intersected a wall-motion abnormality, this would underestimate global stroke work and overestimate E_{ES} .

The ESPVR has been observed to exhibit nonlinearity and dependence on afterload and is not a perfect measure of contractility [17]. We observed that the slope of the ESPVR increased at low EDV, also indicating nonlinearity and load-dependence. We observed that ESPVR tended towards greater convexity at increased inotropy.

Golden angle MRI allowed us to retrospectively reconstruct images from a single experiment with variable exposure time and frame rate to optimally determine temporal resolution. In a previous validation study of radial real-time MRI [18], 80 projections were reconstructed per image frame, with $T_{ex} = 200$ ms and $T_{fr} = 66$ ms; however, we found these parameters were not sufficiently short to accurately measure LV volume at elevated heart rates.

Limitations

There are additional challenges to assessment of load-independent LV function in patients. Clinical use is hampered by the need for noninvasive pressure monitoring of high fidelity, accurate and continuous monitoring of LV volumes and the need to vary loading conditions by vena caval occlusion or the use of vasoactive drugs [19]. Investigators have utilized the high spatial resolution of MRI to address the second of these challenges by the ‘single-beat’ approach [20] or by quantification of aortic flow using real-time velocity encoded CMR as described above [16, 21, 22]. These methods are attractive for clinical and preclinical studies, but may be insufficient for estimation of regional cardiac contractility or LV

contractility in the presence of shunt or mitral regurgitation, which may often occur in ischemic heart disease.

Summary

In summary, we validated a method to measure LV contractile function using real-time MRI-derived PV relations. This method has the potential to be used in studies of heart disease to assess regional contractile function in preclinical studies.

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Figure 1. Method for real-time MR measurement of LV PV loops

a, time-varying LV volume. 4 chamber and 2 chamber views of the segmentation (red) are overlaid on a cine images. **b**, single-slice real-time MR image at mid-ventricle. **c**, 1D profile intersecting the septum. A white line indicates the location of the 1D projection in **b**. The occlusion time is indicated with a black bar in **c** and **d**. **d**, LV pressure is matched synchronously to each radiofrequency pulse. **e**, the ratio of the slice volume in **b** to the global LV volume in **a**. The time-varying error in the slice to volume ratio is shown in red. Peak error is labeled in green. **f**, the PV loop, derived from 2D real-time MRI and scaled to LV volumes using ratio in **e**.

Figure 2. Dependence of measured heart function on exposure time T_e under rest and stress physiology

a, EDV was the lower-right corner of the PV loop. **b**, ESV was the upper-left corner of the PV loop. **c**, EF was calculated from **a** and **b**. **d**, time-varying volume under stress conditions for $T_e = 72.8, 162.4$ and 560 ms and with continuous breathing **e**, PV loops for cine and real-time acquisitions for $T_e = 72.8$ and 560 ms. **f**, **g**, image frames at end-diastole and at end-systole with segmented volume overlay for $T_e = 72.8$ and 560 ms. Error is the std. across 10 end-expiratory heartbeats. Solid black lines indicate cine data.

Figure 3. Dependence of observed EDV, ESV and EF on temporal resolution T_r under rest and stress physiology

a, EDV was the lower-right of the PV loop. **b**, ESV was the upper-left corner of the PV loop

c, EF was calculated from a and b. Error is the std. across 10 end-expiratory heartbeats.

Solid black lines indicate cine data.

Figure 4. Real-time PV loops from a swine under rest and stress physiology

a, PV loops were measured at rest and during continuous dobutamine infusion. LV pressure obtained with an intraventricular catheter was synchronized with each radiofrequency pulse.

b, time-varying LV pressure and **c**, LV volume during 12 s of continuous acquisition.

Figure 5. Real-time PV loops from a swine under rest and stress conditions during a preload reduction experiment

a, time-varying LV pressure and **b**, LV volume during 12 s of continuous acquisition throughout the preload reduction experiment. **c**, PV loops were measured at rest and at increased inotropic state. The ESPVR was fit with a quadratic function (solid red line) through ES points (green points). **d**, 1d projection intersecting the LV parallel to the LV outflow tract. **e**, 1d profile (mri m-mode image) of LV, RV, and septum from the projection of the real-time data in **d**. Occlusion and release times are indicated with white lines.

Figure 6. Myocardial stroke work under rest and stress conditions during a preload reduction experiment

a, time-varying stroke work during transient reduction in EDV and release. **b**, relationship between stroke work and edv (preload-recruitable stroke work). **c**, relationship between stroke work, edv and inotropic state.

Table 1

	Real time ($T_e = 95.2$ ms, $T_r = 2.8$ ms)		Cine	
Hemodynamic Variables	rest (n=5)	inotropic stress (n=5)	rest (n=5)	inotropic stress (n=5)
Heart rate, bpm	112.1 $\pm$ 22.9 *	140.2 $\pm$ 20.2 *	116.8 $\pm$ 21.1	147.6 $\pm$ 16.1
EDV _{LV} , mL	57.9 $\pm$ 13.2	47.0 $\pm$ 5.2	61.1 $\pm$ 10.7	54.1 $\pm$ 5.7
ESV _{LV} , mL	35.3 $\pm$ 7.1 *	23.6 $\pm$ 4.1 *	35.8 $\pm$ 8.0	25.3 $\pm$ 10.7
SV _{LV} , mL	22.7 $\pm$ 8.3	23.4 $\pm$ 7.5	25.3 $\pm$ 5.8	28.9 $\pm$ 3.7
EF _{LV} , %	38.0 $\pm$ 9.0 *	49.0 $\pm$ 11 *	41.0 $\pm$ 7.0	53.0 $\pm$ 3.0
CO _{LV} , L/min	2.6 $\pm$ 0.7	3.2 $\pm$ 0.9	2.9 $\pm$ 0.6	3.3 $\pm$ 1.0
LV Properties				
E _{ED} (mmHg/mL)	0.30 $\pm$ 0.13	0.28 $\pm$ 0.19		
E _{ES} (mmHg, linear model)	1.9 $\pm$ 0.7 *	3.1 $\pm$ 0.3 *		
V ₀ (mL) (linear model)	-8.1 $\pm$ 13.8	-1.9 $\pm$ 4.1		
Stroke work (mmHg mL)	221.3 $\pm$ 51.9 *	306.9 $\pm$ 96.4 *		
PRSW (mmHg)	6.2 $\pm$ 1.2	9.1 $\pm$ 0.9		

* $P < 0.05$ paired t-test