Original Article

Cardiac MRI

A New Gold Standard for Ventricular Volume Quantification During High-Intensity Exercise

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Background—Accurate measures are critical when attempting to distinguish normal from pathological changes in cardiac function during exercise, yet imaging modalities have seldom been assessed against invasive exercise standards. We sought to validate a novel method of biventricular volume quantification by cardiac MRI (CMR) during maximal exercise.

Methods and Results—CMR was performed on 34 subjects during exercise and free-breathing with the use of an ungated real-time (RT-ungated) CMR sequence. ECG and respiratory movements were retrospectively synchronized, enabling compensation for cardiac cycle and respiratory phase. Feasibility of RT-ungated imaging was compared with standard exercise CMR imaging with ECG gating (gated); accuracy of RT-ungated CMR was assessed against an invasive standard (direct Fick); and reproducibility was determined after a second bout of maximal exercise. Ventricular volumes were analyzed more frequently during high-intensity exercise with RT-ungated compared with gated CMR (100% versus 47%; $P<0.0001$) and with better interobserver variability for RT-ungated (coefficient of variation=1.9% and 2.0% for left and right ventricular stroke volumes, respectively) than gated (coefficient of variation=15.2% and 13.6%; $P<0.01$). Cardiac output determined by RT-ungated CMR proved accurate against the direct Fick method with excellent agreement (intraclass correlation coefficient, $R=0.96$), which was highly reproducible during a second bout of maximal exercise ($R=0.98$).

Conclusions—When RT-ungated CMR is combined with post hoc analysis incorporating compensation for respiratory motion, highly reproducible and accurate biventricular volumes can be measured during maximal exercise. (***Circ Cardiovasc Imaging*. 2013;6:329-338.**)

Key Words: cardiac function ■ cardiac output ■ exercise ■ MRI ■ reproducibility

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Exercise performance is dependent on a number of interrelated circulatory, metabolic, hormonal, and muscular factors. Of these, cardiac function may be of primary importance,[1,2] and investigators have sought to associate variance in exercise capacity with changes in cardiac function during exercise (cardiac reserve). In a substantial proportion of patients, significant exertional breathlessness is associated with seemingly normal or only subtly deranged cardiac measures when imaging is performed in the resting state. It may be that abnormalities in cardiac function are coincident with symptoms; however, appraisal of this hypothesis requires an imaging technique in which accuracy is maintained throughout exercise. Moreover, the majority of research has focused on the left ventricle (LV) and systemic circulation as the dominant source of circulatory limitation; however, there is increasing recognition that the pulmonary circulation and right ventricle (RV) may be of equal or even greater importance during exercise.[3] Thus, to direct patient-specific therapies addressing potential heterogeneity in heart failure pathophysiology, there is a need for an imaging technique capable of accurately assessing both cardiac ventricles during exercise.

Clinical Perspective on p 338

Cardiac MRI (CMR) represents the current gold standard in the noninvasive measurement of biventricular volumes in the resting state,[4,5] but there are significant challenges when these techniques are used during exercise. Typically, excellent temporal and spatial resolution is obtained with CMR as a result

Received August 20, 2012; accepted December 7, 2012.

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The online-only Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.112.980037/-/DC1.

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of acquiring data over a number of cardiac cycles, a process that requires constancy of heart rate (HR) and cardiac position. However, during exercise, it is difficult to obtain a reliable ECG signal (because of magneto-hydrodynamic turbulence), and vigorous respiration causes cardiac translation. In combination, these factors cause blurring or ghosting of images collated across cardiac cycles and spatial planes. As a result, investigators have resorted to CMR imaging during early recovery,[6,7] during breath-hold,[8] or at submaximal exercise intensities.[9] No studies have validated real-time exercise CMR measures against cardiac output (CO) measures derived by invasive standards.

We developed a method of CMR acquisition and analysis that enables cine images to be acquired during intense exercise without ECG gating but with retrospective synchronization to cardiac and respiratory cycles. We sought to validate this novel imaging technique comprehensively by assessing feasibility against current standard CMR techniques, accuracy against invasive reference measures of CO, and reproducibility of interobserver and repeated exercise measures.

Methods

The study was performed in 3 stages: (1) a pilot phase in which the feasibility and reproducibility of an ECG-gated rapid acquisition sequence, typical of that used in previous exercise CMR studies (gated), were compared with a new method of real-time ungated image acquisition (ungated-RT), (2) a validation phase in which CO derived by the ungated-RT method was compared with CO derived by an invasive standard (the direct Fick method), and (3) an assessment of reproducibility final stage in which each subject repeated maximal exercise after resting for 1 hour.

The study protocol conformed to the Declaration of Helsinki and was approved by the local ethics committee. All patients provided informed consent.

Subjects

Fifteen healthy subjects (13 male, 2 female) volunteered to participate in the pilot phase. All subjects performed some regular exercise, and 4 subjects were competitive athletes.

A separate cohort of 19 volunteers (17 male, 2 female) participated in the validation and reproducibility phases: 10 healthy competitive athletes (athletes), 6 competitive or ex-competitive athletes with symptomatic ventricular arrhythmias (arrhythmia patients), and 3 patients investigated for exertional breathlessness with a normal LV ejection fraction at rest (heart failure patients).

Exercise Protocol

Pilot Phase

Subjects performed exercise while lying within the bore of the CMR using a cycle ergometer with adjustable electronic resistance (Lode, Groningen, the Netherlands). CMR images were obtained in the resting state and then at 2 exercise workloads: low intensity, a level perceived as easy exercise corresponding to HR of 100 to 120 bpm, and high intensity: a level perceived to be hard but less than maximal and corresponding to a HR between 140 and 170 bpm. Each stage was maintained for ≈6 minutes (1 minute to achieve steady-state and 4 and 5 minutes of image acquisition). At all stages, images were acquired during free-breathing.

Validation Phase

This phase consisted of cardiopulmonary testing and exercise CMR. Cardiopulmonary testing was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany) with an incremental protocol beginning at 50 W and increasing progressively (25 W/min) until exhaustion. Breath-by-breath analysis of the volume and concentration of expired gases was achieved with the use of an automated system with a paramagnetic oxygen analyzer and an infrared carbon dioxide analyzer after calibration against a standardized gas solution. The main outcome measures were oxygen consumption at rest (VO_2 rest), oxygen consumption at maximal exercise (VO_2 max), and maximal power output in Watts.

Exercise CMR was performed ≈24 hours later. Before exercise, a 7F pulmonary artery catheter was inserted into the internal jugular vein and guided under fluoroscopy to the proximal right main pulmonary artery, and a 20-gauge arterial catheter was placed in the radial artery. These catheters were then attached to pressure transducers and a hemodynamic monitor (Maglife Serenity, Schiller AG, Baar, Switzerland), thus enabling the collection of arterial and mixed venous blood samples for the determination of CO by the direct Fick equation. As for the pilot study, subjects performed supine exercise within the CMR bore using the programmable ergometer. Images were acquired during free-breathing at rest and then at 25%, 50%, and 66% of the maximal power wattage as determined by the testing on the previous day. These workloads will subsequently be referred to as rest and low, moderate, and maximal intensity. Each stage of exercise was maintained for ≈3 to 4 minutes, 1 minute to achieve a physiological steady-state and 2 to 3 minutes for image acquisition. We had previously determined that 66% of the maximal power during upright cycling corresponded to maximal exercise in a supine position, in a manner similar to that of previous investigators.[10]

Reproducibility Phase

A third bout of exercise was performed after a delay of 1 hour. The same exercise protocol (rest and low, moderate, and maximal intensity) was repeated after the subject rested for 1 hour.

CMR Equipment, Image Acquisition, and Analysis

Images were acquired with a Philips Achieva 1.5-T CMR with a 5-element phased-array coil (Philips Medical Systems, Best, the Netherlands). The ECG was recorded with a hemodynamic monitor (Maglife Serenity) and converted to an optical trigger input for the CMR. This was preferred to the vector ECG system of the vendor, which was unable to provide an acceptable ECG signal during exercise.

Two acquisition sequences were used:

Gated: retrospective-gated steady-state free-precession cine imaging was performed with 13 to 18 contiguous 8-mm slices in a short-axis (SAX) plane followed immediately by 11 to 15 contiguous 8-mm slices in a horizontal long-axis (HLA) plane. Imaging parameters were as follows: field of view, 320×260 mm (approximately); matrix, 256×256; flip angle, 60°; sensitivity encoding (SENSE) factor, 2 (Cartesian k-space undersampling); repetition time, 2.2 milliseconds; echo time, 1.1 milliseconds; reconstructed voxel size, 1.33×1.33×8 mm; and temporal resolution, 34 milliseconds. The time required for image acquisition (1 retrospectively gated cardiac cycle at each slice) was 50 to 70 seconds for a stack of cine loops in the SAX plane and 45 to 60 seconds for an HLA stack.

Ungated-RT: steady-state free-precession cine imaging was performed without cardiac gating. Forty to 75 consecutive frames were acquired every 36 to 38 milliseconds at each of 13 to 18 contiguous 8-mm slices in the SAX plane, and 50 consecutive frames were acquired at approximately the same temporal resolution for 11 to 15 contiguous 8-mm slices in the HLA plane. Imaging parameters were as follows as follows: field of view, 320×260 mm (approximately); matrix, 128×128; flip angle, 50°; SENSE factor, 2 (Cartesian k-space undersampling); repetition time, 1.8 milliseconds; echo time, 0.9 milliseconds; and reconstructed voxel size, 2.3×2.3×8 mm. The time required for ungated-RT image acquisition could be adapted according to the number of image repetitions defined for each slice. Although it is possible to minimize scan time by acquiring only as many frames as required to include a complete cardiac cycle in each slice (as little as ≈15 seconds for 18 slices during exercise), we programmed sufficient frame repetitions to include at least 1 respiratory cycle (for accurate gating of cardiac translation). A reducing number of repetitions was programmed for each increase in exercise intensity. Thus, as subjects became increasingly tachypneic during exercise, scan duration could be reduced while enabling sufficient data to include multiple cardiac

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Table. Subject Characteristics for the 19 Subjects in the Validation Study and the Change in Measures at Rest Compared With Peak Exercise

	Athletes (n=10)		Arrhythmia Patients (n=6)		Heart Failure Patients (n=3)	
Age, y	35±9		38±26		63±13§	
Body mass index, kg/m^2	22.7±1.3		25.7±3.5		24.4±4.5	
Maximal power upright, W	370±66		304±60‡		97±55§	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Heart rate, bpm	59±14	164±10†	61±12	152±27†	69±5	104±16*§
LV end-diastolic volume, mL	232±31	225±28	224±29	226±23	132±24§	142±26§
RV end-diastolic volume, mL	247±44	229±52	220±34	226±31	141±45§	148±44‡
LV end-systolic volume, mL	91±19	67±15†	102±37	80±36*	48±13‡	48±14
RV end-systolic volume, mL	106±25	77±34†	101±37	88±39	61±44	58±34
LV stroke volume, mL	141±17	158±22*	122±25‡	145±25*	83±12§	94±12*§
RV stroke volume, mL	141±22	154±26*	118±20‡	139±29	80±4§	90±11§
LV ejection fraction ,%	61±4	70±5†	55±8	66±8†	64±4	67±4
RV ejection fraction, %	57±4	67±8†	55±10	62±14*	60±16	63±11
Cardiac output, L/min	8.4±2.6	25.4±4.5†	7.2±1.3	21.6±5.7†	5.6±0.3	9.4±1.2*§
Exercise power, W	0	230±35†	0	175±50†‡	0	53±49†§
Vo_2, mL/min	365±98	4040±696†	364±73	3222±668†‡	274±55	1269±416*§
Hemoglobin, g/dL	13.6±0.7	14.9±0.8*	14.5±0.5	15.1±0.7	13.8±1.5	13.6±1.7
pH arterial	7.41±0.02	7.38±0.04	7.41±0.01	7.38±0.04	7.47±0.04‡	7.44±0.03
O_2 saturation, %	97.9±1.2	96.4±3.7	98.1±0.8	97.2±1.5	98.9±0.2	96.8±3.6
Pao_2, mm Hg	101.8±12.8	92.7±20.3	96.3±11.9	93.4±16.4	112±14.0	99±33.0
Arterial oxygen content, mL O_2/100 mL	17.9±1.1	19.3±1.4*	19.0±6.1	19.7±9.2	18.5±2.1	17.8±1.8
Venous oxygen content, mL O_2/100 mL	13.4±1.3	6.1±1.7†	14.3±6.7	7.2±3.7*	13.5±2.3	6.3±3.0*

LV indicates left ventricular; and RV, right ventricular.

*P<0.05, †P<0.001 for difference between peak exercise and resting measure.

‡P<0.05, §P<0.001 for difference between the arrhythmia or heart failure group and athletes.

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cycles and at least 1 respiratory cycle. Typically, resting scan durations of ≈120 and ≈90 seconds for the SAX and HLA planes, respectively, were reduced to ≈70 and ≈50 seconds at peak exercise. For the patients with heart failure, the duration of scanning was substantially reduced to accommodate their reduced exercise endurance (40–50 seconds for the SAX plane and 30–40 seconds for the HLA plane).

Simultaneous to image acquisition, a plethysmograph was placed on the upper abdomen, providing data on the timing of respiration, which, in combination with the ECG data, was sampled at 500 Hz, enabling the images to be synchronized with these physiological data for offline analysis.

Images were analyzed on a software program developed in-house (RightVoL–Right Volume Leuven, Leuven, Belgium), in which the physiological data (respiratory movement and ECG trigger) were synchronized to the images so that contouring could be performed at the same point in the respiratory cycle, thereby greatly minimizing cardiac translation error (Figure 1). LV and RV endocardial contours were then manually traced on the SAX image, and the points of transection with the HLA plane were indicated, thus enabling constant referencing of the atrioventricular valve plane (Figure 2). Trabeculations and papillary muscles were considered part of the ventricular blood pools, and volumes were calculated by a summation of disks. Stroke volume (SV) was measured as the difference between end-diastolic volume and end-systolic volume, whereas CO was calculated as (RVSV+LVSV/2)×HR.

Calculation of CO by the Direct Fick Method

CO was calculated by the direct Fick method (CO_{Fick}) as VO_2 divided by the arteriovenous oxygen difference (C_a–C_v). The Vo_2 was obtained from the cardiopulmonary test, and the blood gases were collected during the maximal exercise bout within the CMR the next day (Incompatibilities between the cardiopulmonary testing equipment and the CMR environment precluded simultaneous measures). Hemoglobin (Hb), oxygen saturation (O_2 sats), and oxygen partial pressure ($Pao_2$and PVO_2 for arterial and venous respectively) were measured with an automated blood gas analyzer (ABL 700, Radiometer, Copenhagen, Denmark) from samples taken from the pulmonary artery and radial arterial catheters during exercise. The oxygen content in arterial and venous blood (C_a and C_v, respectively) was calculated according to the following equation: C=Hb (mg/dL)×O_2 sats (%)×1.36×10+0.0032×Po_2 (mm Hg).

Statistical Analysis

Gaussian distribution of all continuous variables was confirmed with a Kolmogorov-Smirnov test, and values are reported as mean±SD. A 2-tailed value of P<0.05 was considered significant. Statistical analysis was performed using SPSS version 16.0 software.

Categorical data were compared by use of the Fisher exact test. Differences between baseline and peak exercise measures were analyzed with a paired t test, whereas comparisons between imaging modalities during exercise were performed with a repeated measures ANOVA.

Interobserver variability was tested in the pilot data set between a primary observer (A.L.G.) and 1 of 2 observers (G.C. or A.V.d.B.). The mean value of the 2 observations (x) and the absolute value of the difference between observations (e) ±SD were determined. Reproducibility was assessed by the coefficient of variation (CV) as (e/x) 100%; the 95% limits of agreement, as x±1.96SD. In each case, the 95% limits of agreement as described by Bland and Altman[11] were adjusted with a random-effects model to estimate the within-subject variance after adjustkejt for the mean on each measurement occasion, as described by Myles and Cui.[12] Agreement between observers and

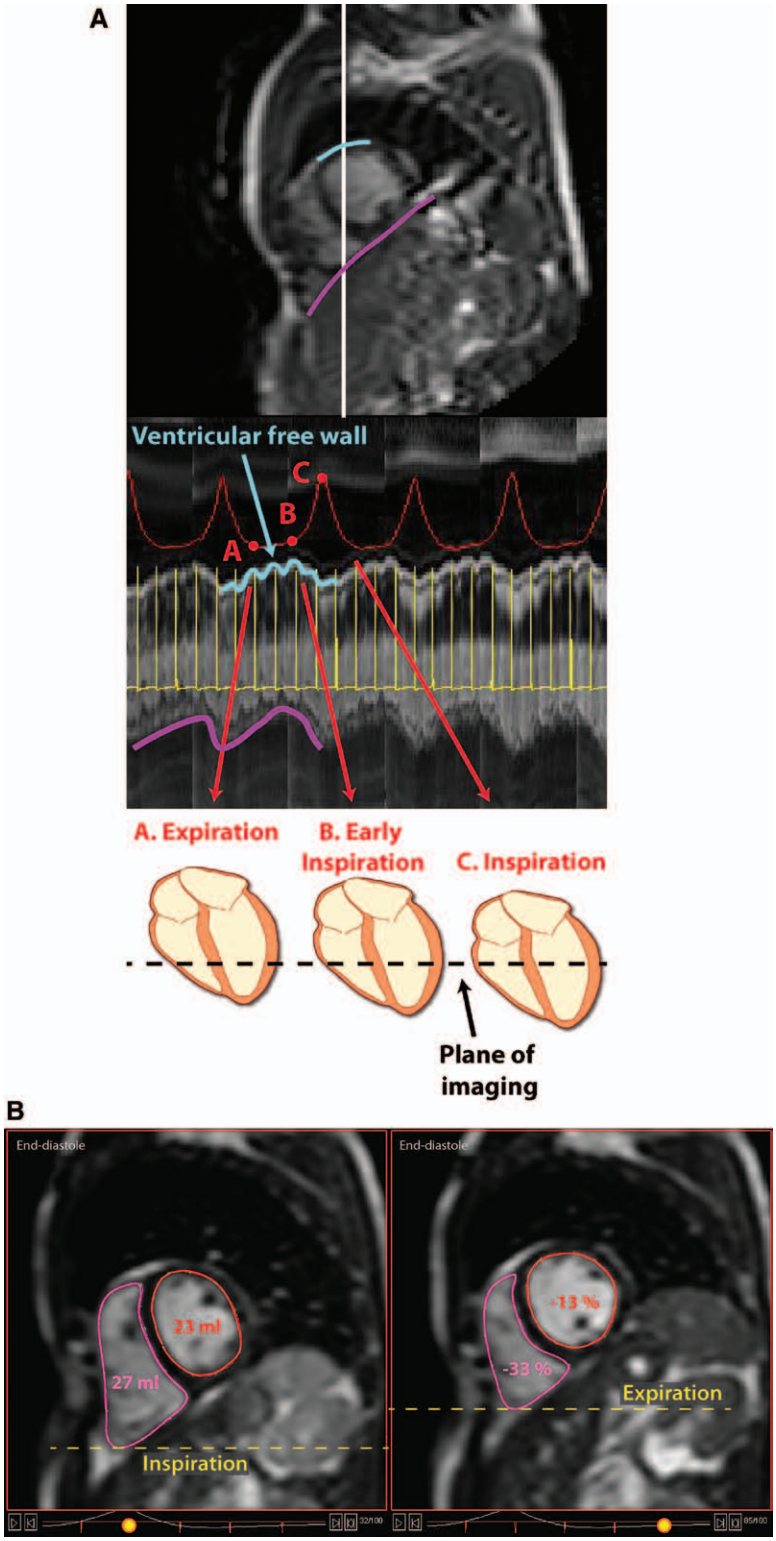

Figure 1. **A**, Synchronization of physiological and imaging data to compensate for cardiac translation during exercise. Traces from the plethysmograph (red) and ECG trigger (yellow) were retrospectively synchronized with the cardiac MRI (CMR) images as illustrated with a 1-dimensional (M-mode) sample of the image set. Inspiration is associated with an increase in the plethysmograph pressure (point **C**) and inferior movement of both the diaphragm (highlighted in purple) and the heart (the anteroseptal left ventricular wall highlighted in blue). The ventricle (highlighted in blue) contracts after each ECG trigger but also moves down with the diaphragm during inspiration. All volumetric analyses were performed at a standardized point in the respiratory cycle so that the cardiac translation was effectively neutralized. The cartoon highlights the potential error introduced by respiratory movement. The heart translates through each plane of imaging so that a midventricular slice may be incorrectly acquired more apically or basally during expiration or inspiration, respectively. **B**, Single-slice cardiac volumes measured during peak inspiration and peak expiration. The yellow dotted lines demonstrate the cardiac translation tangential to the imaging plane, whereas the change in volumes implies translation through the imaging plane with expiration being associated with a 33% and 13% reduction in right ventricular and left ventricular volumes, respectively.

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methods was further assessed by use of the intraclass correlation coefficient (R) as calculated with a 2-way mixed models for the absolute difference between measures, as described by Shrout and Fleiss.[13]

Results

Pilot Phase

The 15 subjects (age, 31±5 years; body mass index, 23.1±3.2 kg/m^2) all completed the exercise protocol, but analyzable images were more frequently obtained with the RT-ungated sequence than by the gated sequence (P<0.0001). Good-quality images were obtained at rest and during exercise in all subjects with RT-ungated CMR. In contrast, excessive artifact in the ECG signal during high-intensity exercise precluded image acquisition in 3 subjects with gated CMR, whereas images were of insufficient quality for analysis in another 5 subjects. In 4 of these 8 subjects, analyzable images were obtained

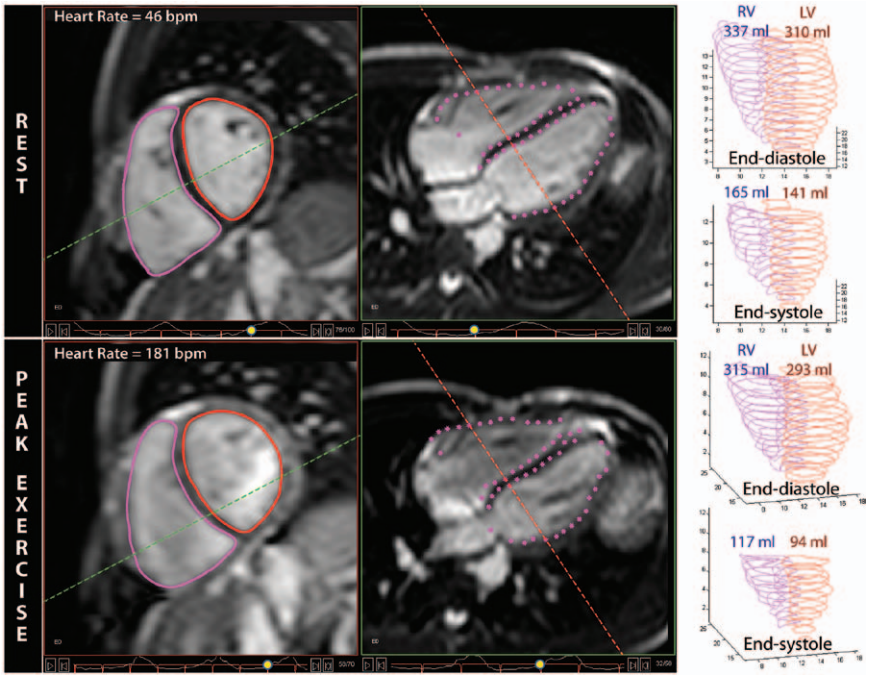

Figure 2. Example of real-time ungated cardiac MRI imaging at rest and during maximal exercise. The short-axis plane is used to define the endocardial contours. The point at which these transect the horizontal long-axis plane is indicated by the software (pink dots), enabling the atrioventricular level to be accurately defined. Having standardized cardiac translation attributable to respiration, the agreement between the 2 planes is excellent, with the endocardial traces in the short-axis plane transecting the endocardial border in the horizontal long-axis plane at rest and during exercise. In this professional cyclist with marked cardiomegaly, the stroke volume of 199 mL at peak exercise (181 bpm) equated to a cardiac output of 36 L/min. LV indicates left ventricle; and RV, right ventricle.

during low- but not high-intensity exercise, whereas in the remainder, no analyzable images were obtained during exercise. A comparison of typical gated and RT-ungated images is provided in Video I in the online-only Data Supplement.

Figure 3 illustrates the superior agreement between observers when determining SV with the RT-ungated sequence for the LV (Figure 3A) and RV (Figure 3B). When LVSV was determined by gated CMR, the CV increased from rest to low- and high-intensity exercise (5.7% versus 12.9% versus 15.2%, respectively), whereas when RT-ungated CMR was used, the CV remained low throughout exercise (5.0% versus 1.0% versus 1.9%; P=0.001 for intermethod comparison). Similarly, RVSV agreement was inferior with gated CMR (CV=5.4% versus 16.3% versus 13.6%) compared with RT-gated CMR (4.8% versus 3.8% versus 2.0%; P=0.007).

Validation Phase

Resting and exercise measures for the 19 subjects are summarized in the Table. The heart failure patients were older and had markedly reduced CO, Vo_2, and HRs at maximal exercise compared with the athlete and arrhythmia groups. As may be expected for supine compared with upright exercise, the maximal HR during supine cycling within the CMR was less than that during the upright cycle cardiopulmonary testing (150±27 versus 165±30 bpm; P<0.0001). LV and RV end-diastolic volumes at peak exercise were unchanged relative to baseline values, whereas LV and RV end-systolic volumes decreased in the athlete and arrhythmia groups but not in the heart failure patients. Consequently, ejection fraction increased in the athletes and patients with arrhythmias but not in those with heart failure. In all groups, there was a marked reduction in PVO_2 consistent with the expected increase in peripheral muscle extraction. The combination of increased O_2 delivery and extraction resulted in an increase in O_2 consumption, which ranged from an 11-fold increase in athletes to a more modest 4.6-fold increase in heart failure subjects.

There was excellent agreement (intraclass correlation coefficient=0.96) and modest variability (CV=17.5%) between CO derived by RT-ungated CMR and CO derived by the direct Fick method (Figure 4). There was a slight bias, with larger CO measures being obtained by the Fick method. At rest, this bias was very slight (0.43 L/min, representing 5.5% of mean volumes), but CO_{FICK} increased to a greater extent than CO_{CMR} (P<0.0001 for the interaction between exercise CO and method), so the differences were more appreciable at peak exercise (3.65 L/min, 15.2% of mean volumes).

Reproducibility Phase

There was no significant change in the multiple measures of CO throughout exercise when CMR was repeated (P=0.12 for the interaction between exercise CO and trial). As illustrated in Figure 5, there was excellent reproducibility with an overall intraclass correlation coefficient (R) of 0.98, which was similarly strong if each phase of exercise was assessed separately (rest R=0.86, low-intensity R=0.98, moderate-intensity R=0.98, and maximal-intensity R=0.94).

Discussion

By combining RT-ungated CMR with post hoc analysis incorporating compensation for respiratory motion, we have defined a means of measuring biventricular volumes during exercise that is highly reproducible and accurate. CO calculated in this manner is comparable with that obtained by the direct Fick method but offers significant advantages. Exercise CMR avoids the need for arterial and central venous sampling and, through assessment of changes in RV and LV volumes, provides a more complete description of ventricular filling, ejection, and interventricular interaction during exercise. This is particularly relevant to pathologies of the RV and pulmonary circulation that are challenging to assess by other imaging modalities.

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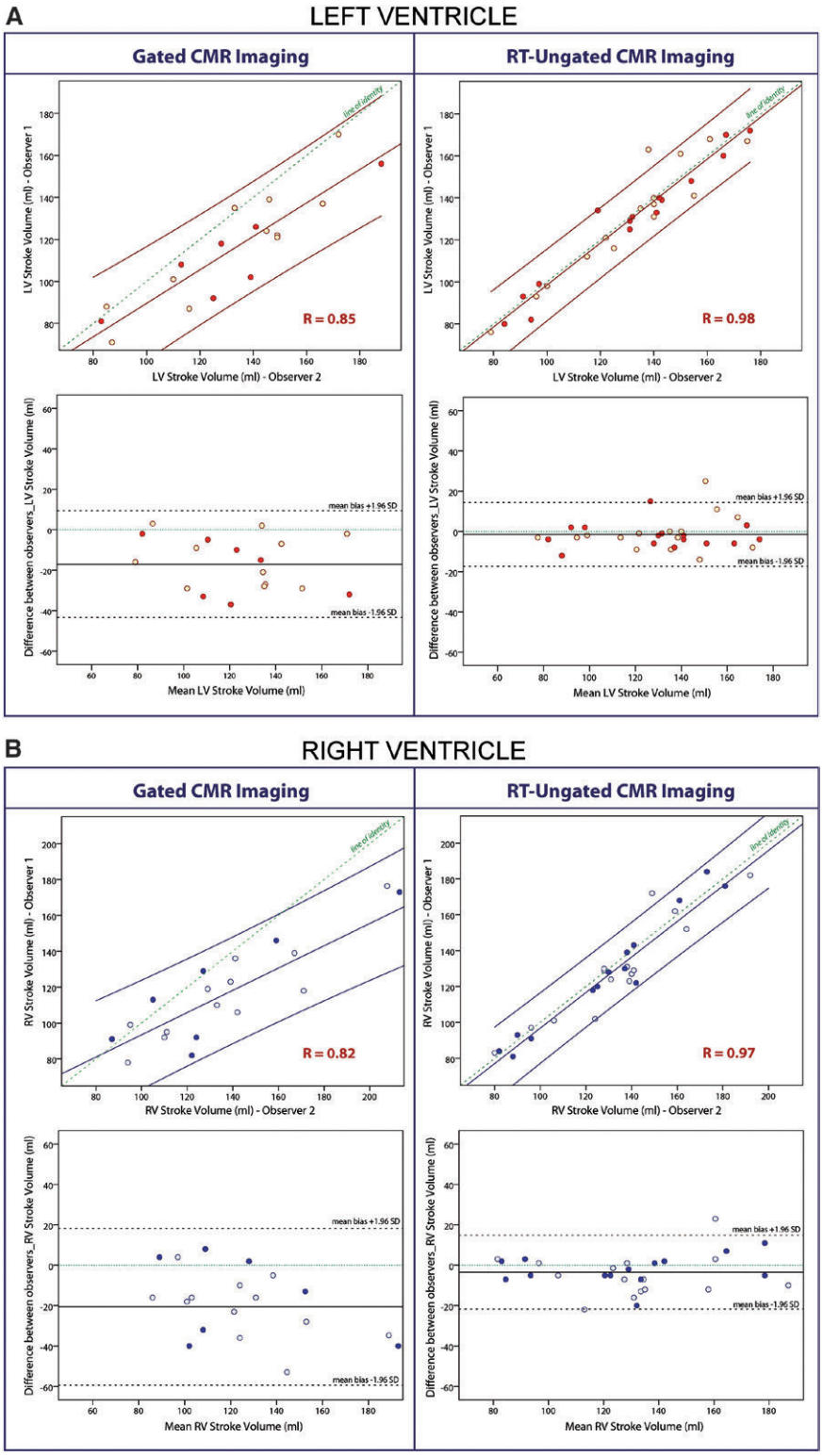

Figure 3. Interobserver variability for quantification of left ventricular (LV; **A**) and right ventricular (RV; **B**) stroke volumes by gated compared with ungated images. Linear regressions with intraclass correlation coefficients (**top**) and Bland–Altman plots (**bottom**) illustrating superior agreement with the real-time ungated cardiac MRI (CMR) method. Data are presented for images acquired during low-intensity exercise (◦) and high-intensity exercise (•) comparing stroke volumes measured by 2 observers. With the use of gated CMR, images from low- and high-intensity exercises were unable to be analyzed in 4 of 15 and 8 of 15 subjects, respectively, whereas all exercise time points could be analyzed in all subjects with RT-ungated CMR. In the Bland–Altman plots, the mean bias and 95% limits of agreement (±1.96 SD) are presented.

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Gated CMR Is Unsuitable for Real-Time Exercise Measures

Although previous investigators have combined gated CMR with exercise to provide important pathophysiological insights into disease processes, studies have been performed at relatively low levels of exertion, during exercise cessation, and during breath-holds.[6–8,10] We attempted to use these techniques during high-intensity exercise and free-breathing but were unable to obtain images suitable for analysis in more than half of the subjects. Even when images were obtained, the gating of images resulted in considerable artifacts. Gating across multiple cardiac cycles provides data from similar time points in the cardiac cycle, but respiratory motion results in summation of image data from differing cardiac positions,

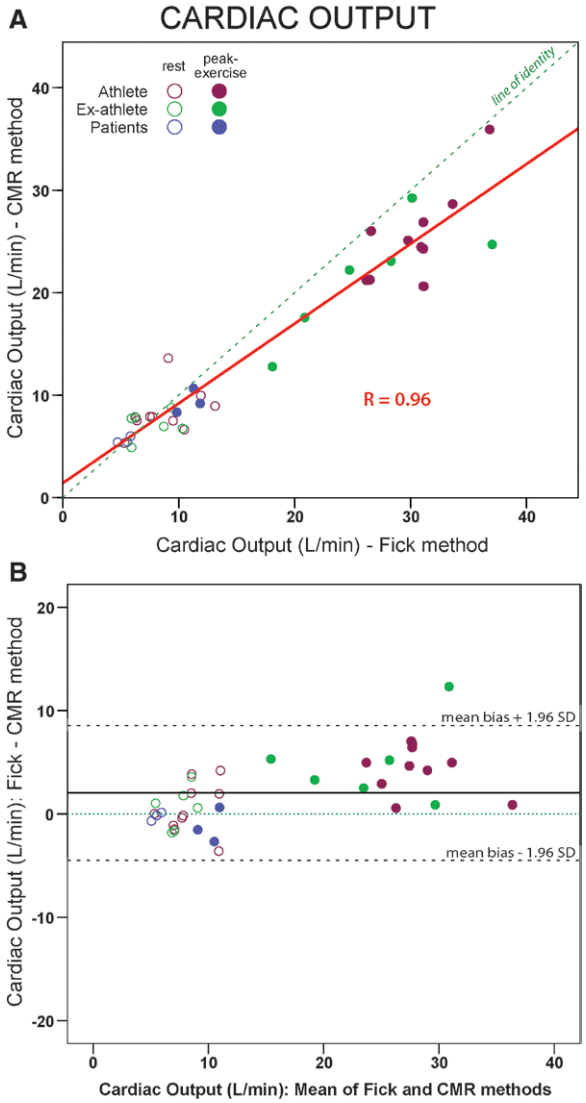

Figure 4. Comparison between cardiac outputs derived by real-time ungated cardiac MRI (CMR) and by the direct Fick method. Linear regressions with intraclass correlation coefficients (**A**) and Bland–Altman plots (**B**) of resting (◦) and peak exercise data (•).

producing blurring and ghosting of images (Video I in the online-only Data Supplement). In contrast, ungated-RT CMR acquires images like a video, with every frame representing a complete data set independent of the ECG or respiratory cycle, thus avoiding these summation artifacts. As a result, we demonstrated that ungated RT-CMR was more feasible and that volumetric measures were far more reproducible. As a final advantage, ungated-RT CMR offers greater flexibility in sequence programming. Because the number of frames acquired at each slice is reduced, scan duration can be substantially reduced, making it suitable for real-time exercise scanning in patients with markedly impaired exercise tolerance.

Exercise CMR Is a Highly Accurate and Reproducible Technique

Our methodology proved highly accurate against CO derived by the Fick method. There was an extremely strong correlation between CO derived by the 2 methods that remained strong when peak exercise values were considered in isolation (Figure 4). Overall, CO measures obtained by Fick were greater than by CMR, especially at peak exercise. This is likely explained by the fact that CO_{FICK} was derived from oxygen consumption values obtained at the instantaneous point of maximal exertion. In contrast, the CMR volume measures require the subject to maintain a maximal level of exertion for ≈90 seconds. Thus, the bias between techniques may, at least in part, represent true differences in CO resulting from the limitations of measuring instantaneous CO by CMR.

The excellent reproducibility (interobserver and repeated tests) of exercise CMR was demonstrable despite the fact that there was a number of analysis stages, each with the potential to increase variability. First, the data were manually gated to respiration by use of the plethysmograph trace. Second, the appropriate phases of the cardiac cycle were selected, and finally the contours were traced in a SAX plane, while simultaneously referencing the HLA plane. We believe that optimization of each of these steps contributed to the accuracy of our technique. As demonstrated in Figure 1A and Video II in the online-only Data Supplement, respiration is associated with a downward translation of the diaphragm and heart such that these structures translate through the plane of imaging during image acquisition. Thus, single-slice volumes increased with inspiration and decreased with expiration (Figure 1B), which may be caused by physiological differences in preload attributable to the fall in intrathoracic pressures during inspiration and cardiac translation through the imaging plane. Thus, there is the potential for a random error to be introduced that may cancel or become additive dependent on the chance selection of respiratory phase. As far as we are aware, this is the first description of a technique for standardizing the confounding influences of cardiac translation and respiratory alterations in preload. In addition, we found that it was extremely helpful to simultaneously cross-reference imaging planes. A majority of studies have used SAX images for ventricular volume assessments because the endocardial borders are clearest when they are transected by the imaging plane.[14] However, there are also advantages in using long-axis planes because they provide the most accurate definition of the atrio-ventricular level, where volumetric errors can be considerable.[15,16] Our analysis software combines the advantages of both, enabling maximum endocardial contrast while simultaneously defining the valvular planes (always after compensation for respiratory translation). In this manner, accurate volumetric measures could be obtained during strenuous exercise in patients with poor cardiac reserve and in athletes with supernormal cardiac reserve.

Although we assert that the accuracy of our technique is enhanced by the novel method incorporating retrospective respiratory gating and biplane referencing for defining endocardial contours, it is important to note that we have not compared the accuracy of our technique with and without the inclusion of these factors. Thus, we cannot quantify the relative importance of these factors in the overall accuracy. Rather, we sought to address all of the theoretical confounders in volume assessment during exercise with the aim of defining the most accurate and reproducible technique to date.

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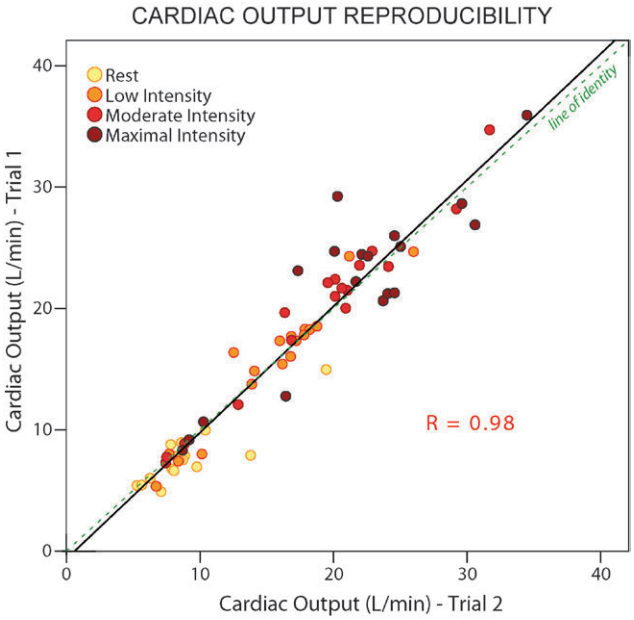

Figure 5. Reproducibility of repeated testing. Cardiac output derived by real-time–ungated cardiac MRI at rest and during 3 stages of exercise is compared with measures obtained after a repeat bout of exercise 1 hour later.

Current Standards of Biventricular Assessment During Exercise

Biventricular assessment during exercise has been attempted with radionuclide ventriculography and echocardiography, but both have significant limitations.[17] Radionuclide ventriculography requires gating over many cardiac cycles, and careful optimization of the imaging planes is required to minimize overlap of radiotracer counts between cardiac chambers. Moreover, this technique results in significant radiation exposure for the patient. Cardiac volumes can be estimated by echocardiography from a single cardiac cycle with Doppler flow methods or 2-dimensional areas. However, significant geometric assumptions are required in extrapolating data to a 3-dimensional volume; this is especially true of the complex RV. As a consequence, conclusions on exercise-induced cardiac changes have the potential to be influenced as much by the limitations of the imaging technique as by the underlying pathophysiology. For example, it was reported that, in contrast to healthy subjects, patients with heart failure and preserved ejection fraction failed to increase end-diastolic LV volumes during exercise, thus promoting the concept that exercise intolerance was a result of LV filling impairment.[18] However, when assessed with echocardiography rather than radionuclide ventriculography, the opposite changes in ventricular volumes have been demonstrated.[19]

A number of investigators have sought to capitalize on the potential advantages of CMR imaging during exercise. Roest et al[10] used an ultrafast gated CMR imaging technique similar to that used in the pilot phase of our study. To avoid the failed acquisitions and poor image quality that we encountered, they imaged during a brief cessation in cycling and with breath-holds. Thus, image acquisition was actually performed during a brief period of recovery, which may help explain why the CO measured at maximal exercise in healthy young subjects was approximately half that report here. Holverda et al[6,7] used gated CMR after patients performed moderate-intensity exercise outside the magnet bore. These techniques were sufficient for demonstrating a difference in RV reserve between patients with marked alterations in RV afterload and healthy control subjects, although the expected differences in recovery rates serve as an important confounder. Lurz et al[9,20] provide the only previous experience of true real-time CMR imaging during exercise and free-breathing using an ungated sequence similar to that described here (although they used radial rather than Cartesian k-space sampling). We provide advances on these novel techniques by instituting a means of compensating for cardiac translation caused by diaphragmatic excursion and by validating the techniques against a recognized standard. Furthermore, Lurz et al[9,20] used an ergometer in which subjects move their straight legs in a kicking motion, a form of exercise that uses a smaller muscle mass and less physical work (≤22.5 W) compared with the cycle exercise used in our study (218±52 W). Higher CO values were measurable in our study, and the strong agreement between CO_{Fick} and CO_{CMR} verifies their accuracy. In 1 subject, a professional cyclist, we measured a CO_{CMR} of 36 L/min, which, to the best of our knowledge, is the highest directly measured CO reported.

Clinical Implications

Perhaps the greatest potential utility for exercise CMR imaging is to define the contribution of the presystemic circulation to overall cardiac performance. Holverda et al[6,7] demonstrated that RVSV should increase during exercise as a consequence of reductions in RV end-systolic volume but that this did not occur in patients with increased RV afterload. Similarly, reduced RV reserve has been reported in patients with pulmonary valve pathology[20] and global cardiomyopathies.[21] Thus, reduced RV contractility, increased RV afterload, or both can explain attenuated CO response and the resulting

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premature fatigue during exercise. These presystemic factors may even be important determinants of exercise capacity in trained athletes, in whom excesses in RV wall stress have been associated with specific RV fatigue after prolonged strenuous exercise.[22,23] Thus, the RV may be of particular importance to exercise performance, the full extent of which can now be appraised with accuracy.

Thus far, exercise CMR has found a niche in imaging the RV during exercise attributable to the fact that RV quantification is difficult with alternative imaging modalities. However, the excellent accuracy and reproducibility are at least as good for LV measures, thus providing the ideal tool for separating normal from abnormal cardiac reserve in subtle cardiomyopathies. Although our initial experience includes only a few patients with markedly reduced cardiac reserve, we demonstrate that the technique is flexible in its application and is accurate across a broad range of exercise capacities.

Limitations

We compared exercise CMR measures and those derived by the direct Fick method in the absence of a true gold standard measure of CO. Although the relative accuracy of all measures of circulatory flow have been debated,[17] the direct Fick method is a frequently referenced standard, and its derivation is completely independent from that of direct cardiac volume measures. In addition, the components used for the calculation of CO_{Fick} (Vo_2 max and blood gases) were acquired during separate bouts of maximal exercise with differences in body position and duration of exercise. However, previous investigators have demonstrated that body position does not influence Vo_2 max results[24] and that values are highly reproducible across a range of exercise durations.[25]

We did not formally measure postprocessing times; however, our current methodology is quite labor intensive. With ungated-RT CMR images, a period of ≈30 minutes is required to measure end-diastolic and end-systolic volumes for both ventricles at any given stage of exercise. Slightly less time is required for analyzing gated images at rest, but at higher levels of exercise, difficulties in identifying the endocardium make this at least as time-consuming, if not impossible. There is potential for considerable time savings in the analysis of ungated CMR because the quality of the images makes them very suitable for automated segmentation and contour detection.

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Acknowledgments

We wish to thank Ann Belmans for her assistance with the statistical analysis.

Sources of Funding

This study was funded by a grant from the Fund for Scientific Research Flanders (FWO), Belgium. Dr La Gerche is funded by a postdoctoral scholarship from the National Health and Medical Research Council of Australia (NHMRC). The authors would like to thank Rotary International Tienen, Belgium for their contribution toward the CMR ergometer purchase.

Disclosures

None.

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CLINICAL PERSPECTIVE

Exercise intolerance defines many cardiac disease processes, yet cardiac imaging is most frequently performed at rest. In heart failure patients, abnormalities in cardiac function may be subtle or absent at rest but apparent under physiological stress. However, the increased diagnostic potential of exercise imaging may be realized only if functional measures can be performed and remain robust throughout exercise. In this article, we describe a novel MRI technique, real-time ungated cardiac MRI (RT-ungated CMR), for measuring biventricular volumes during high-intensity exercise. Compared with an invasive reference technique, we demonstrate that RT-ungated CMR is feasible, reproducible, and accurate in a wide range of subjects, from patients with markedly reduced cardiac reserve to athletes with supernormal outputs during exercise. RT-ungated CMR represents a new gold standard in imaging during exercise that enables a comprehensive assessment of biventricular filling and emptying at the time when cardiac output demand starts to exceed capacity. Therefore, the technique provides unique insight into cardiac constraints in both health and disease. This may be of particular value for the right ventricle, which is difficult to assess with other imaging modalities but is an important determinant of prognosis in conditions affecting the pulmonary vasculature, including pulmonary hypertension secondary to left heart failure. RT-ungated CMR is an ideal tool for selecting heart failure patients who may derive the greatest benefit from therapies targeting the right ventricle and pulmonary circulation. The accuracy of RT-ungated CMR may also facilitate the diagnosis of evolving or subclinical cardiomyopathies secondary to diabetes mellitus, hypertension, or anthracyclines.

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