Cardiac Magnetic Resonance Imaging: A New Gold Standard for Ventricular Volume Quantification During High-Intensity Exercise

La Gerche et al: Exercise Cardiac Magnetic Resonance

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DOI: 10.1161/CIRCIMAGING.112.980037

Journal Subject Codes: [30] CT and MRI; [125] Exercise testing
Abstract

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 magnetic resonance imaging (CMR) during maximal exercise.

Methods and Results—CMR was performed on 34 subjects during exercise and free-breathing using an ungated real-time CMR (“RT-ungated”) 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 following a second bout of maximal exercise. Ventricular volumes were able to be analyzed more frequently during high-intensity exercise using RT-ungated as compared with gated CMR (100% vs. 47%, p<0.0001) and with better inter-observer variability for RT-ungated (coefficient of variation CV=1.9% and 2.0% for left and right ventricular stroke volumes, respectively) than gated (CV=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 secondbout of maximal exercise (R=0.98).

Conclusions—By combining real-time ungated CMR with post-hoc analysis incorporating compensation for respiratory motion, highly reproducible and accurate biventricular volumes can be measured during maximal exercise.

Key Words: magnetic resonance imaging, cardiac function, exercise, reproducibility, cardiac output
Exercise performance is dependent upon a number of inter-related circulatory, metabolic, hormonal and muscular factors. Of these, cardiac function may be of primary importance\textsuperscript{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, but appraisal of this hypothesis requires an imaging technique in which accuracy is maintained throughout exercise. Moreover, a majority of research has focused on the LV and systemic circulation as the dominant source of circulatory limitation but there is increasing recognition that the pulmonary circulation and RV may be of equal, or even greater importance during exercise\textsuperscript{3}. Thus, in order 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.

Cardiac magnetic resonance imaging (CMR) represents the current gold-standard in non-invasive measurement of biventricular volumes in the resting state\textsuperscript{4,5} but there are significant challenges when using these techniques during exercise. Typically, excellent temporal and spatial resolution are obtained with CMR as a result of acquiring data over a number of cardiac cycles, a process which requires constancy of heart rate and cardiac position. However, during exercise it is difficult to obtain a reliable electrocardiographic signal (due to 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\textsuperscript{6,7}, during breath-hold\textsuperscript{8} or at sub-maximal exercise intensities\textsuperscript{9}. There are no
studies that have validated real-time exercise CMR measures against cardiac output measures derived by invasive standards.

We developed a method of CMR acquisition and analysis which enables cine images to be acquired during intense exercise without ECG gating but with retrospective synchronization to cardiac and respiratory cycles. We sought to comprehensively validate this novel imaging technique by: 1) assessing feasibility against current standard CMR techniques, 2) accuracy against invasive reference measures of cardiac output (CO), and 3) reproducibility of inter-observer and repeated exercise measures.

Methods

The study was performed in three 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’) was compared against 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 against 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 and all patients provided informed consent.

Subjects

15 healthy subjects (13 males, 2 females) 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 left ventricular ejection fraction at rest (“heart failure patients”).

Exercise protocol

Pilot phase: subjects performed exercise whilst 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 two exercise workloads: 1) “low-intensity”: a level perceived as easy exercise corresponding to heart rate of 100-120 bpm, and 2) “high-intensity”: a level perceived to be hard, but less than maximal and corresponding to a heart rate between 140 – 170 bpm. Each stage was maintained for approximately 6 minutes (1 minute to achieve steady-state and 4 - 5 minutes of image acquisition). At all stages, images were acquired during free breathing.

Validation phase: consisted of cardiopulmonary testing and exercise CMR. Cardiopulmonary testing was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany) using an incremental protocol commencing at 50W and increasing progressively (25 W/minute) until exhaustion. Breath-by-breath analysis of the volume and concentration of expired gases was achieved using an automated system with a paramagnetic oxygen analyzer and an infrared carbon dioxide analyzer following calibration against a standardized gas solution. The main outcome measures were oxygen consumption at rest (VO_{2rest}), oxygen consumption at maximal exercise (VO_{2max}) and maximal power output in Watts.
Exercise CMR was performed approximately 24 hours later. Prior to exercise, a 7 Fr pulmonary artery catheter was inserted in 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 determination of cardiac output 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 previous day’s testing. These workloads will subsequently be referred to as rest, low-, moderate- and maximal-intensity. Each stage of exercise was maintained for approximately 3 - 4 minutes, 1 minute to achieve a physiological steady-state and 2 -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 with a delay of one hour. The same exercise protocol (rest, low-, moderate- and maximal-intensity) was repeated after the subject rested for one hour.

CMR equipment, image acquisition and analysis

Images were acquired using a Philips Achieva 1.5T CMR with a five-element phased-array coil (Philips Medical Systems, Best, The Netherlands). The ECG was recorded using a hemodynamic monitor (Maglife Serenity, Schiller AG, Baar, Switzerland) and converted to
an optical trigger input for the CMR. This was preferable to the vendor’s own vector ECG system which was unable to provide an acceptable ECG signal during exercise.

Two acquisition sequences were used:

‘Gated’: retrospective-gated steady state free precession (SSFP) cine imaging was performed with 13-18 contiguous 8mm slices in a short-axis (SAX) plane followed immediately by 11-15 contiguous 8 mm slices in a horizontal long-axis (HLA) plane. Imaging parameters were: field of view 320 x 260mm (approximately), 256 x256 matrix, flip angle 60°, SENSE factor 2 (Cartesian k-space under-sampling), repetition time 2.2msec, echo time 1.1msec, reconstructed voxel size 1.33 x 1.33 x 8mm, temporal resolution 34msec. The time required for image acquisition (1 retrospectively gated cardiac cycle at each slice) was 50-70 secs for a stack of cine loops in the SAX plane and 45 – 60 secs for a HLA stack.

‘Ungated-RT’: SSFP cine imaging was performed without cardiac gating. 40 - 75 consecutive frames were acquired every 36-38msecs at each of 13 –18 contiguous 8mm slices in the SAX plane and 50 consecutive frames were acquired at approximately the same temporal resolution for 11 –15 contiguous 8mm slices in the HLA plane. Imaging parameters were: field of view 320 x260mm (approximately), 128 x128 matrix, flip angle 50°, SENSE factor 2 (Cartesian k-space under-sampling), repetition time 1.8msec, echo time 0.9msec, reconstructed voxel size 2.3 x 2.3 x 8mm. 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 so as to include at least one respiratory cycle (for accurate gating of cardiac translation). A reducing number of repetitions were programmed...
for each increase in exercise intensity. Thus, as subjects became increasingly tachypneic during exercise, scan duration could be reduced whilst enabling sufficient data to include multiple cardiac cycles and at least one respiratory cycle. Typically, resting scan durations of ~120 and ~90 secs for the SAX and HLA planes respectively were reduced to ~70 and ~50 secs at peak exercise. For the patients with heart failure, the duration of scanning was substantially reduced so as to accommodate their reduced exercise endurance (40 – 50 secs for the SAX plane and 30-40 secs 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 500Hz enabling the images to be synchronized with this physiological data for offline analysis.

Images were analyzed on an in-house developed software program (RightVoL – Right Volume Leuven, Leuven, Belgium) in which the physiological data (respiratory movement and ECG trigger) was synchronized to the images such that contouring could be performed at the same point in the respiratory cycle, thereby greatly minimizing cardiac translation error (see 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 atrio-ventricular valve plane (see 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 (EDV) and end-systolic volume ( ESV) whilst CO was calculated as \((RVSV + LVSV / 2) \times \text{heart rate (HR)}\).
Calculation of cardiac output by the Direct Fick method

CO was calculated by the direct Fick method (CO\textsubscript{Fick}) as VO\textsubscript{2} divided by the arteriovenous oxygen difference (C\textsubscript{a} – C\textsubscript{v}). The VO\textsubscript{2} was obtained from the cardiopulmonary test and the blood gases were collected during the maximal exercise bout within the CMR the following day (incompatibilities between the cardiopulmonary testing equipment and the CMR environment precluded simultaneous measures). Hemoglobin (Hb), oxygen saturation (O\textsubscript{2} sats) and oxygen partial pressure (PaO\textsubscript{2}) were measured using 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\textsubscript{a} and C\textsubscript{v} respectively) was calculated according to the equation: C =Hb (mg/dL) x O\textsubscript{2} sats (%) x 1.36 x10 +0.0032 x PaO\textsubscript{2} (mmHg).

Statistical analysis

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

Categorical data was compared using the Fisher’s exact test. Differences between baseline and peak-exercise measures were analyzed using a paired t-test whilst comparisons between imaging modalities during exercise was performed using a repeated measures ANOVA.

Inter-observer variability was tested in the pilot data set between a primary observer (ALG) and one of two observers (GC or AVDB). The mean value of the two observations (x) and the absolute value of the difference between observations (e) ±SD were determined. Reproducibility was assessed by the coefficient of variation CV = (e/x) 100%, the 95% limits of agreement x ± 1.96SD. In each case, the 95% limits of agreement as described by Bland...
and Altman\textsuperscript{11} were adjusted using a random effects model to estimate the within-subject variance after adjusting for the mean on each measurement occasion, as described by Myles and Cui\textsuperscript{12}. Agreement between observers and methods was further assessed using the intraclass correlation coefficient (R) as calculated using a two-way mixed models for the absolute difference between measures, as described by Shrout and Fleiss\textsuperscript{13}.

**Results**

**Pilot phase:** The 15 subjects (31±5 years, body mass index 23.1±3.2) all completed the exercise protocol but analyzable images were more frequently obtained using 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 using RT-ungated CMR. In contrast, excessive artifact in the ECG signal during high intensity exercise precluded image acquisition in 3 subjects using gated CMR whilst images were of insufficient quality for analysis in a further 5 subjects. In 4 of these 8 subjects, analyzable images were obtained during low- but not high-intensity exercise, whilst in the remainder no analyzable images were obtained during exercise. A comparison of typical gated and RT-ungated images is provided in Video 1.

Figure 3 illustrates the superior agreement between observers when determining SV using 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% vs. 12.9% vs. 15.2%, respectively) whereas using RT-ungated CMR the CV remained low throughout exercise (5.0% vs. 1.0% vs. 1.9%), p = 0.001 for inter-method comparison. Similarly, RVSV agreement was inferior using gated CMR (CV = 5.4% vs. 16.3% vs. 13.6%) when compared with RT-gated CMR (4.8% vs. 3.8% vs. 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 heart rates at maximal exercise, as compared to the athlete and arrhythmia groups. As may be expected for supine as 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 bpm vs. 165±30 bpm, p<0.0001). LV and RV EDV at peak exercise were unchanged relative to baseline values whereas LV and RV ESV decreased in the athlete and arrhythmia groups but not in the heart failure patients. Consequently, ejection fraction (EF%) 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 (intra-class correlation coefficient = 0.96) and modest variability (CV=17.5%) between CO derived by RT-ungated CMR and 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 (+0.43L/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) such that 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
intra-class correlation coefficient (R = 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 real-time ungated CMR with post-hoc analysis incorporating compensation for respiratory motion, we have defined a means of measuring biventricular volumes during exercise which is highly reproducible and accurate. CO calculated in this manner is comparable to 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 inter-ventricular interaction during exercise. This is particularly relevant to pathologies of the RV and pulmonary circulation which are challenging to assess by other imaging modalities.

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/ or 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 able to be 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 producing blurring and “ghosting” of images (see Video 1). In contrast, ungated-RT
CMR acquires images like a video, with every frame representing a complete dataset independent of the ECG or respiratory cycle, thus avoiding these summation artifacts. As a result, we demonstrated that not only was ungated RT-CMR more feasible, volumetric measures were far more reproducible. As a final advantage, ungated-RT CMR offers greater flexibility in sequence programming. By reducing the number of frames acquired at each slice, 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 two methods which 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 approximately 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 (inter-observer and repeated tests) of exercise CMR was demonstrable in spite of there being a number of analysis stages, each with the potential to increase variability. Firstly, the data was manually ‘gated’ to respiration using the plethysmograph trace. Secondly, the appropriate phases of the cardiac cycle were selected, and finally the contours were traced in a SAX plane whilst 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 2, 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 through physiological differences in preload due to the fall in intra-thoracic pressures during inspiration as well as cardiac translation through the imaging plane. Thus, there is the potential for a random error to be introduced which 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 as these provide the most accurate definition of the atrio-ventricular (AV) level where volumetric errors can be considerable\(^{15,16}\). Our analysis software combines the advantages of both, enabling maximum endocardial contrast whilst 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 super-normal cardiac reserve.

Whilst we assert that the accuracy of our technique is enhanced by the novel method incorporating retrospective respiratory gating and bi-plane 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.

Current standards of biventricular assessment during exercise

Biventricular assessment during exercise has been attempted using 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 using Doppler flow methods or 2D areas. However, significant geometric assumptions are required in extrapolating data to a 3D volume, and this is especially true of the complex RV. As a consequence, conclusions regarding exercise-induced cardiac changes have the potential to be influenced as much by the limitations of the imaging technique as the underlying pathophysiology. For example, it was reported that, in contrast to healthy subjects, patients with heart failure and preserved ejection fraction (HFPEF) 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.\(^ {10}\) employed an ‘ultra-fast’ gated CMR imaging technique similar to that employed 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 and this may help explain why the CO measured at ‘maximal exercise’ in healthy young subjects was approximately half that which we report here. Holverda et al. 6, 7 used gated CMR after patients performed moderate intensity exercise outside of the magnet bore. These techniques were sufficient for demonstrating a difference in RV reserve between patients with marked alterations in RV afterload as compared with healthy controls, 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 a similar ungated sequence 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 through diaphragmatic excursion and by validating the techniques against a recognized standard. Furthermore, Lurz et al. used an ergometer in which subjects move their straight legs in a kicking motion, a form of exercise which utilizes a smaller muscle mass and less physical work (< 22.5 W) as 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 one subject, a professional cyclist, we measured a CO_{CMR} of 36 l/min which, to our knowledge, is the highest directly measured CO to have been reported.

Clinical implications

Perhaps the greatest potential utility for exercise CMR imaging is to define the contribution of the pre-systemic circulation to overall cardiac performance. Holverda et al. demonstrated that RV SV should increase during exercise as a consequence of reductions in RV ESV but that this did not occur in patients with increased RV afterload 6, 7. 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 resulting premature fatigue during exercise. These pre-systemic 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 following prolonged strenuous exercise. 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 due to the fact that RV quantification is difficult using alternative imaging modalities. However, the excellent accuracy and reproducibility is 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 to those derived by the direct Fick method in the absence of a true “gold standard” measure of CO. Whilst the relative accuracy of all measures of circulatory flow have been debated, the direct Fick method is a frequently referenced standard and its derivation is completely independent from that of direct cardiac volume measures. Also, the components used for the calculation of CO\text{Fick} (VO_{2}\text{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}\text{max} results and that values are highly reproducible across a range of exercise durations.
We did not formally measure post-processing times however our current methodology is quite labor intensive. Using ungated-RT CMR images, approximately 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 as the quality of the images make them very suitable for automated segmentation and contour detection.

Acknowledgements

The authors wish to thank Ann Belmans for her assistance with statistical expertise.

Sources of Funding

This study was funded by a grant from the Fund for Scientific Research Flanders (FWO), Belgium. A. La Gerche is funded by a post-doctoral scholarship from the National Health and Medical Research Council of Australia (NHMRC).

Disclosures

None.

References


Table. Subject characteristics for the 19 subjects in the validation study and the change in measures at rest as compared with peak-exercise.

<table>
<thead>
<tr>
<th></th>
<th><strong>Athletes (n=10)</strong></th>
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<th><strong>Heart failure patients (n=3)</strong></th>
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<tr>
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<td><strong>Exercise</strong></td>
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</tr>
<tr>
<td>pH arterial</td>
<td>7.41 ±0.02</td>
<td>7.38 ±0.04</td>
<td>7.41 ±0.01</td>
</tr>
<tr>
<td>O$_2$ saturation (%)</td>
<td>97.9 ±1.2</td>
<td>96.4 ±3.7</td>
<td>98.1 ±0.8</td>
</tr>
<tr>
<td>PaO$_2$ (mmHg)</td>
<td>101.8 ±12.8</td>
<td>92.7 ±20.3</td>
<td>96.3 ±11.9</td>
</tr>
<tr>
<td>Arterial oxygen content (ml O$_2$/100ml)</td>
<td>17.9 ±1.1</td>
<td>19.3 ±1.4*</td>
<td>19.0 ±6.1</td>
</tr>
<tr>
<td>Venous oxygen content (ml O$_2$/100ml)</td>
<td>13.4 ±1.3</td>
<td>6.1 ±1.7†</td>
<td>14.3 ±6.7</td>
</tr>
</tbody>
</table>

* p < 0.05, † p < 0.001 for difference between peak-exercise as compared with resting measure;
‡ p < 0.05, § p < 0.001 for difference between the arrhythmia or heart failure groups as compared with athletes.
Figure Legends

Figure 1a. 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 CMR images as illustrated using a one-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 antero-septal LV wall highlighted in blue). The ventricle (highlighted in blue) contracts following 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 such that the cardiac translation was effectively neutralized. The cartoon below highlights the potential error introduced by respiratory movement. The heart translates through each plane of imaging such that a mid-ventricular slice may be incorrectly acquired more apically or basally during expiration or inspiration, respectively.

Figure 1b. Single slice cardiac volumes measured during peak inspiration and peak expiration. The yellow dotted lines demonstrate the cardiac translation tangential to the imaging plane whilst the change in volumes imply translation through the imaging plane with expiration being associated with a 33% and 13% reduction in RV and LV volumes respectively.

Figure 2. Example of real-time ungated CMR 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 atrio-ventricular level to be accurately defined. Having standardized cardiac translation due to respiration, the agreement between the two planes is excellent with the endocardial traces in the SAX plane transecting the endocardial border in the HLA plane at rest and during exercise. In this professional cyclist with marked cardiomegaly the stroke volume of 199ml at peak exercise (181 bpm) equated to a cardiac output of 36 l/min.

**Figures 3a and 3b. Inter-observer variability for quantification of left ventricular (a) and right ventricular (b) stroke volumes by gated as compared with ungated images.** Linear regressions with intraclass correlation coefficients (above) and Bland-Altman plots (below) illustrating superior agreement using the RT-ungated CMR method. Data is presented for images acquired during low-intensity exercise (open circles) and high-intensity exercise (closed circles) comparing stroke volumes measured by two observers. Using gated CMR, images from low- and high-intensity exercise were unable to be analyzed in 4/15 and 8/15 subjects respectively, whereas all exercise time points could be analyzed in all subjects using RT-ungated CMR. In the Bland-Altman plots the mean bias and 95% limits of agreement (± 1.96 SD) are presented.

**Figure 4. Comparison between cardiac outputs derived by RT-ungated CMR and by the direct Fick method.** Linear regressions with intraclass correlation coefficients (a) and Bland-Altman plots (b) of resting (open circles) and peak exercise data (closed circles).

**Figure 5. Reproducibility of repeated testing.** Cardiac output derived by RT-ungated CMR at rest and during 3 stages of exercise is compared with measures obtained following a repeat bout of exercise one hour later.
LEFT VENTRICLE

Gated CMR Imaging

RT-Ungated CMR Imaging

LV Stroke Volume (ml) - Observer 1

LV Stroke Volume (ml) - Observer 2

LV Stroke Volume (ml) - Observer 1

LV Stroke Volume (ml) - Observer 2

Difference between observers_LV Stroke Volume (ml)

Difference between observers_LV Stroke Volume (ml)

Mean LV Stroke Volume (ml)

Mean LV Stroke Volume (ml)
RIGHT VENTRICLE

Gated CMR Imaging

RT-Ungated CMR Imaging

$R = 0.82$

$R = 0.97$

Difference between observers, RV Stroke Volume (ml)

Mean bias ±1.96 SD

Difference between observers, RV Stroke Volume (ml)

Mean bias ±1.96 SD
CARDIAC OUTPUT REPRODUCIBILITY

- Rest
- Low Intensity
- Moderate Intensity
- Maximal Intensity

$R = 0.98$

Cardiac Output (L/min) - Trial 2 vs. Cardiac Output (L/min) - Trial 1

Line of identity

Circulation
Cardiovascular Imaging
Journal of the American Heart Association
Cardiac Magnetic Resonance Imaging: A New Gold Standard for Ventricular Volume Quantification During High-Intensity Exercise
Andre La Gerche, Guido Claessen, Alexander Van De Bruaene, Nele Pattyn, Johan Van Cleemput, Marc Gewillig, Jan Bogaert, Steven Dymarkowski, Piet Claus and Hein Heidbuchel

_Circ Cardiovasc Imaging_. published online December 17, 2012;
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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SUPPLEMENTAL MATERIAL

**Video 1.** Comparison of exercise CMR images using the gated and RT-ungated acquisition sequences.

**Video 2.** RT-ungated image acquisition demonstrating the same slice as used for volume quantification in Figure 1a. The video demonstrates substantial cardiac translation and reduced volume measures during expiration despite volumes being measured in the same imaging plane.