BJR


Received: 6 December 2014 | Revised: 27 January 2015 | Accepted: 23 February 2015

doi: 10.1259/bjr.20140831

Cite this article as:
Moody WE, Edwards NC, Chue CD, Taylor RJ, Ferro CJ, Townend JN, et al. Variability in cardiac MR measurement of left ventricular ejection fraction, volumes and mass in healthy adults: defining a significant change at 1 year. Br J Radiol 2015;88:20140831.

## SHORT COMMUNICATION

# Variability in cardiac MR measurement of left ventricular ejection fraction, volumes and mass in healthy adults: defining a significant change at 1 year

**[1,2]W E MOODY, MRCP, [1,2]N C EDWARDS, MRCP, PhD, [1,2]C D CHUE, MRCP, PhD, [1,2]R J TAYLOR, MRCP, [3]C J FERRO, MD, FRCP, [2]J N TOWNEND, MD, FRCP and [2]R P STEEDS, MD, FRCP**

[1]Birmingham CardioRenal Group, Centre for Clinical Cardiovascular Sciences, University of Birmingham, Edgbaston, Birmingham, UK
[2]Department of Cardiology, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, UK
[3]Department of Nephrology, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, UK

Address correspondence to: Dr William E Moody
E-mail: *william.moody@nhs.net*

**Objective:** Variability in the measurement of left ventricular (LV) parameters in cardiovascular imaging has typically been assessed over a short time interval, but clinicians most commonly compare results from studies performed a year apart. To account for variation in technical, procedural and biological factors over this time frame, we quantified the within-subject changes in LV volumes, LV mass (LVM) and LV ejection fraction (EF) in a well-defined cohort of healthy adults at 12 months.

**Methods:** Cardiac MR (CMR) was performed in 42 healthy control subjects at baseline and at 1 year (1.5 T Magnetom® Avanto; Siemens Healthcare, Erlangen, Germany). Analysis of steady-state free precession images was performed manually offline (Argus software; Siemens Healthcare) for assessment of LV volumes, LVM and EF by a single blinded observer. A random subset of 10 participants also underwent repeat imaging within 7 days to determine short-term interstudy reproducibility.

**Results:** There were no significant changes in any LV parameter on repeat CMR at 12 months. The short-term interstudy biases were not significantly different from the long-term changes observed at 1 year. The smallest detectable change (SDC) for LVEF, end-diastolic volume, end-systolic volume and LVM that could be recognized with 95% confidence were 6%, 13 ml, 7 ml and 6 g, respectively.

**Conclusion:** The variability in CMR-derived LV measures arising from technical, procedural and biological factors remains minimal at 12 months. Thus, for patients undergoing repeat annual assessment by CMR, even small differences in LV function, size and LVM (which are greater than the SDC) may be attributed to disease-related factors.

**Advances in knowledge:** The reproducibility and reliability of CMR data at 12 months is excellent allowing clinicians to be confident that even small changes in LV structure and function over this time frame are real.

Cardiac MRI (CMR) is considered the gold standard technique to monitor changes in left ventricular (LV) size and function in congenital and acquired heart disease.[1,2] Reference ranges normalized for gender, age and body surface area help clinicians discriminate between normality and pathology,[3,4] and by including assessments of short-term interstudy variability (test–retest after 1 week) can account for differences in LV measurements arising from physiological variation (load alterations and time-of-day effects). Most clinical imaging, however, is repeated at much greater time intervals; physicians frequently monitor ventricular size and function in patients with valvular heart disease or cardiomyopathy on an annual basis, although there are no longitudinal CMR data quantifying the effect of biological and technical variability over this time frame. Without such information, it is difficult to determine what represents a clinically significant change, particularly when the observed difference is small.

We therefore sought to examine the within-subject changes in LV volumes, LV mass (LVM) and ejection fraction (EF) using CMR over 12 months in a well-characterized cohort of healthy adults.

## METHODS AND MATERIALS

We retrospectively identified 42 healthy control subjects (45 ± 13 years; male, 43%) from the Chronic Renal Impairment in Birmingham–Donor study (CRIB-Donor) who did not proceed to nephrectomy. The CRIB-Donor

study is a prospective, multicentre, parallel group observational study of living kidney donors and healthy controls designed to assess the cardiovascular effects of live kidney donation (NCT01028703). All subjects included in the present study had a 10-year risk of a cardiovascular event of <7.5%, a normal exercise stress echocardiogram and normal haematology and biochemistry blood profiles.[5] Exclusion criteria included any of the following: a history of cardiovascular disease, including hypertension; diabetes; glucose intolerance; chronic kidney disease; or a first degree relative with a proven or potentially inheritable cardiac condition.

### MRI

The full CRIB-Donor study protocol is described in detail elsewhere.[6] Briefly, subjects underwent CMR imaging (1.5 T Magnetom® Avanto; Siemens Healthcare, Erlangen, Germany) at baseline and 12 months. Serial contiguous short axis steady-state free precession (SSFP) cines were piloted from the vertical and horizontal long-axis images of the left and right ventricles [electrocardiogram R wave-gated, SSFP imaging (TrueFISP); temporal resolution, 40–50 ms; repetition time, 3.2 ms; echo time, 1.6 ms; flip angle, 60°; slice thickness, 7 mm with 3-mm gap] in accordance with previously validated methodologies.[4] Analysis of SSFP images was performed manually offline (Argus software; Siemens Healthcare) by a single blinded observer (WEM, 5 years' experience) for the assessment of LVEF, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVM. The LV basal short axis slice was identified as the image containing at least 50% of circumferential myocardium at end diastole. Papillary muscles were included in the mass and excluded from volumetric analyses.

### Reproducibility

To assess intraobserver report variability, baseline studies were reanalysed by the same observer 4 weeks later, blinded to the original data. A random subset of participants ($n = 10$) also underwent repeat imaging within 7 days to determine short-term interstudy reproducibility; both scans were analysed by the same blinded observer.

### Statistical analysis

Data were analysed using SPSS® v. 21 (SPSS Inc., Chicago, IL). Data are expressed as mean ± standard deviation (SD), median (interquartile range) or frequency (%). The normality of distribution was determined using normality plots and the Kolmogorov–Smirnov test. The within-patient changes were compared with a Student's paired *t*-test. The mean short-term change in LV parameters was compared with the mean 12-month change using an unpaired *t*-test.

Reliability was assessed using the intraclass correlation coefficient (ICC) with a model of absolute agreement; absolute measurement error was estimated by the standard error of measurement (SEM) and smallest detectable change (SDC).[7] The SEM is defined as $\mathrm{SEM} = \mathrm{SD}d/\sqrt{2}$, where SD*d* is the SD of the mean difference between two measurements, and takes the amount of measurement error into consideration and quantifies the within-subject variability. The SDC is calculated as $\mathrm{SDC} = 1.96 \times \mathrm{SEM} \times \sqrt{2}$, where 1.96 corresponds to the 95% confidence interval and the square root of 2 is to adjust for sampling from two different measurements and represents the 95% confidence that a change in the measurement exceeding this threshold is true and reliable and not just a measurement error.[7] For all statistical comparisons, $p < 0.05$ was considered significant.

## RESULTS

The demographics and cardiovascular risk profiles of the healthy control subjects identified for this study are presented in Table 1. All subjects remained well with no clinical events over the 12-month study period.

There were no significant changes in any LV parameter on repeat CMR at 12 months (Table 2). Moreover, the short-term interstudy biases (mean differences) were not significantly different from the long-term changes observed at 1 year (LVEF, LVEDV, LVESV, LVM; $p = 0.81$, 0.63, 0.97, 0.72, respectively). On the basis of our interstudy reproducibility, the SDC for LVEF, LVEDV, LVESV and LVM that could be recognized with 95% confidence is 6%, 13 ml, 7 ml and 6 g, respectively (Table 3).

## DISCUSSION

To our knowledge, this is the first longitudinal CMR study to perform a repeat annual assessment in individuals free of cardiovascular disease. The data presented herein suggest the effect of healthy ageing at 1 year is negligible and need not be taken into account by clinicians when reporting CMR studies performed in patients over this time frame.

Table 1. Patient characteristics

| Patients variable | $n = 42$ |
|---|---|
| Age (years) | 45 ± 13 |
| Gender (male : female) | 18 : 24 |
| Height (m) | 1.70 ± 0.90 |
| Weight (kg) | 74.5 ± 11.5 |
| Body mass index ($\mathrm{kg\,m^{-2}}$) | 26.2 ± 4.0 |
| Office systolic blood pressure (mmHg) | 120.7 ± 11.7 |
| Office diastolic blood pressure (mmHg) | 74.1 ± 8.4 |
| Cardiovascular medications | 0 (0) |
| Haemoglobin ($\mathrm{g\,l^{-1}}$) | 135.2 ± 10.2 |
| Estimated glomerular filtration rate $<60\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$ | 0 (0) |
| Fasting cholesterol ($\mathrm{mg\,dl^{-1}}$) | 191.4 ± 40.2 |
| Fasting glucose ($\mathrm{mg\,dl^{-1}}$) | 84.4 ± 7.2 |
| Urinary ACR ($\mu\mathrm{g\,mg^{-1}}$) | 0.89 (0.89–2.65) |
| 10-year cardiovascular risk <7.5%[a] | 42 (100) |

ACR, albumin : creatinine ratio.
Data are expressed as mean ± standard deviation, median (interquartile range) or frequency (%). Dividing the urinary ACR by 8.84 converts the units from micrograms per milligram to milligrams per millimoles.
[a]Joint British Societies (JBS)-3 heart risk calculator available at www.jbs3risk.com.[5]

Table 2. Annual change in left ventricular (LV) ejection fraction (EF), volumes and mass

| Parameter | Month 0 | Month 12 | Mean difference | *p*-value |
|---|---|---|---|---|
| LVEF (%) | 70.3 ± 6.9 | 71.2 ± 6.4 | 0.9 ± 4.3 | 0.18 |
| LV end-diastolic volume (ml) | 121.2 ± 28.2 | 121.3 ± 26.9 | 0.1 ± 10.4 | 0.91 |
| LV end-systolic volume (ml) | 37.0 ± 14.7 | 35.8 ± 13.7 | −1.2 ± 6.6 | 0.26 |
| LV mass (g) | 111.4 ± 31.7 | 109.5 ± 32.0 | −2.0 ± 8.6 | 0.14 |

Data are mean ± standard deviation. Changes in LV parameters were compared using a paired Student's *t*-test.

As for any imaging modality, CMR is subject to variability because of technical, procedural, observer and biological factors.[8] The intrinsic variability of CMR becomes important in interpreting serial tests in order to define a true pathological change in a given patient. Therefore, in order to calculate a SDC for each LV parameter, we opted to include an assessment of short-term interstudy reproducibility. Despite recent improvements in MRI scanner performance and pulse sequences, it has been over a decade since the test–retest (interstudy) reproducibility of LVM and volume measurements made in normal adult subjects using manual contouring has been reported.[9,10] Our interstudy reproducibility was excellent, which may in part reflect implementation of contemporary imaging hardware and potentially improved cine sequences.

For completeness, we present both relative and absolute indices of agreement: ICC and SDC, respectively. However, when interpreting clinical tests, it becomes more intuitive and appropriate to calculate a SDC because this index can account for both random and systematic errors in measurements.[11] The SDC is based on a statistical computation and is distinct from the minimally clinically important difference (MCID) that is set on clinical grounds and represents how large the change in an outcome should be to be deemed clinically important. Establishing a MCID for LV parameters was beyond the scope of the present study.

All images in this study were acquired using a standardized imaging protocol on a single scanner at one centre, conditions that might often be replicated in routine practice. Studies were also performed, however, by the same technician and analysed by a single trained observer, which may approximate less to standard clinical circumstances. Nevertheless, this scenario provides the optimal setting to maximize test–retest reliability and derive the lowest achievable SDC for respective LV parameters. It should also be remembered that as an index of test–retest reliability, the ICC is affected by the characteristics of the individuals being tested and will therefore likely be higher in this healthy cohort than in diseased populations.[10] Indeed, these results may be less generalizable to patients with heart disease where the reliability of SSFP cine imaging may be hampered by gating issues (*e.g.* atrial fibrillation or frequent ectopy) or the inability to perform adequate breath-holds (*e.g.* heart failure).

This study was not designed or indeed powered to examine changes in LV structure or function owing to "normal" ageing; cross-sectional data provided from the Multi-Ethnic Study of Atherosclerosis study suggest that LVM incrementally decreases with increasing age by −0.3 g per year.[12] By contrast, the novelty of the present study lies in its longitudinal design, which has enabled an assessment of within-subject variability of LV functional metrics over a 12-month period. Importantly, the data presented herein demonstrate that in health, the size of any change to the LV parameters observed at 1 year is not significantly different in magnitude to the respective SDC.

## CONCLUSIONS

These data emphasize the reproducibility and reliability of CMR data and have particular importance for the interpretation of routine clinical reports as well as longitudinal research studies.

Table 3. Intraobserver and short-term interstudy variability using cardiac MR in normal healthy adults

| Parameter | Variability | Mean difference | *p*-value | Limits of agreement | Intraclass correlation coefficient (95% confidence interval) | Smallest detectable change |
|---|---|---|---|---|---|---|
| LV ejection fraction (%) | Intraobserver | 1.00 ± 1.27 | 0.11 | −1.48 to 3.48 | 0.99 (0.94–1.00) | – |
| | Interstudy | 0.57 ± 2.94 | 0.63 | −5.19 to 6.33 | 0.93 (0.62–1.00) | 5.8 |
| LV end-diastolic volume (ml) | Intraobserver | 0.67 ± 3.62 | 0.67 | −6.43 to 7.77 | 0.99 (0.95–1.00) | – |
| | Interstudy | −1.57 ± 6.47 | 0.43 | −14.25 to 11.11 | 0.99 (0.97–1.00) | 12.7 |
| LV end-systolic volume (ml) | Intraobserver | −0.83 ± 2.79 | 0.50 | −6.30 to 4.64 | 0.99 (0.93–1.00) | – |
| | Interstudy | −1.29 ± 3.65 | 0.37 | −8.44 to 5.86 | 0.98 (0.91–1.00) | 7.2 |
| LV mass (g) | Intraobserver | −0.33 ± 2.16 | 0.21 | −4.56 to 3.90 | 0.99 (0.95–1.00) | – |
| | Interstudy | −1.00 ± 3.03 | 0.50 | −6.94 to 4.94 | 0.98 (0.91–1.00) | 5.9 |

LV, left ventricular.
Data are mean ± standard deviation. Changes in LV parameters were compared using a paired Student's *t*-test.

In patients undergoing repeat annual assessment by CMR, even small changes in LV function, size and mass (which are greater than the SDC for the given parameter) may be attributable to disease progression and/or a treatment response.

## ACKNOWLEDGMENTS

We are grateful for the statistical support offered by Dr Peter Nightingale. WEM is supported by a British Heart Foundation Clinical Research Training Fellowship (FS/11/17/28700). We are also grateful for the resources provided by the Birmingham NIHR/Wellcome Clinical Research Facility in conducting this study.

## FUNDING

This work was supported by the British Heart Foundation, London, UK.

## REFERENCES

1. Fratz S, Chung T, Greil GF, Samyn MM, Taylor AM, Valsangiacomo Buechel ER, et al. Guidelines and protocols for cardiovascular magnetic resonance in children and adults with congenital heart disease: SCMR expert consensus group on congenital heart disease. *J Cardiovasc Magn Reson* 2013; **15**: 51. doi: 10.1186/1532-429X-15-51
2. Hendel RC, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, et al; American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group; American College of Radiology; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance; American Society of Nuclear Cardiology; North American Society for Cardiac Imaging; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006; **48**: 1475–97.
3. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. *J Cardiovasc Magn Reson* 2005; **7**: 775–82.
4. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2006; **8**: 417–26.
5. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014; **100**(Suppl. 2): ii1–67. doi: 10.1136/heartjnl-2014-305693
6. Moody WE, Tomlinson LA, Ferro CJ, Steeds RP, Mark PB, Zehnder D, et al. Effect of a reduction in glomerular filtration rate after nephrectomy on arterial stiffness and central hemodynamics: rationale and design of the EARNEST study. *Am Heart J* 2014; **167**: 141–149.e2. doi: 10.1016/j.ahj.2013.10.024
7. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res* 2005; **19**: 231–40.
8. Iskandrian AE, Hage FG, Shaw LJ, Mahmarian JJ, Berman DS. Serial myocardial perfusion imaging: defining a significant change and targeting management decisions. *JACC Cardiovasc Imaging* 2014; **7**: 79–96. doi: 10.1016/j.jcmg.2013.05.022
9. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002; **90**: 29–34.
10. Moon JC, Lorenz CH, Francis JM, Smith GC, Pennell DJ. Breath-hold FLASH and FISP cardiovascular MR imaging: left ventricular volume differences and reproducibility. *Radiology* 2002; **223**: 789–97.
11. Vaz S, Falkmer T, Passmore AE, Parsons R, Andreou P. The case for using the repeatability coefficient when calculating test-retest reliability. *PLoS One* 2013; **8**: e73990. doi: 10.1371/journal.pone.0073990
12. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2009; **2**: 191–8. doi: 10.1161/CIRCIMAGING.108.819938