Accuracy of cardiac CT, radionuclide and invasive ventriculography, two- and three-dimensional echocardiography, and SPECT for left and right ventricular ejection fraction compared with cardiac MRI: a meta-analysis

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Aims
Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) are important tools in clinical decision-making. We hypothesized that two-dimensional echocardiography (2DE), three-dimensional echocardiography (3DE), radionuclide ventriculography (RNV), cardiac computed tomography (CT), gated single-photon emission CT (SPECT), and invasive cardiac cine ventriculography (ICV) provide variable accuracy for LVEF and RVEF when using cardiac magnetic resonance imaging (MRI) as a gold standard.

Methods and results
We systematically searched published databases for studies comparing LVEF and RVEF measured by CT, 3DE, 2DE, RNV, ICV, and SPECT compared with MRI. We utilized meta-analytic methods to determine the pooled bias (mean weighted difference), limits of agreement (LOA), and correlation coefficient for each modality. For LVEF, 174 studies (7047 patients) were included. For RVEF, 46 studies (1720 patients) were included. Pooled LOA for LVEF were different between modalities: CT and 3DE had smaller LOA than 2DE, SPECT, ICV, and RNV. 2DE showed the largest LOA and a weaker correlation for LVEF (r = 0.660). For RVEF, CT and 3DE have the best data to support their use with a bias, 5% and tight LOA and correlation coefficients with (r) >0.75.

Conclusion
For LVEF, CT and 3DE had the lowest bias and the best agreement with MRI. Compared with MRI, CT and 3DE comparably estimate RVEF and have the most evidence to support their use.

Keywords
Left ventricular ejection fraction • Right ventricular ejection fraction • Echocardiography • Cardiac computed tomography • Cardiac MRI • Ventriculography

Introduction
Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) are clinically important measures of cardiac function that provide powerful prognostic information and serve to guide therapy in a wide variety of clinical settings. In practice, there are several modalities that are employed to determine LVEF and RVEF. Two-dimensional echocardiography (2DE) is the most widely utilized due to its ease of use, availability, and the absence of ionizing radiation. However, 2DE relies on 2D geometrical assumptions in a single plane (four-chamber or two-chamber view) to estimate ventricular ejection, as does single-plane invasive cardiac cine ventriculography (ICV). These geometric assumptions can be overcome by modalities that acquire more anatomically accurate datasets, such as three-dimensional echocardiography (3DE), radionuclide ventriculography (RNV), single-photon emission computed tomography (SPECT), and cardiac computed tomography (CT).
(SPECT), cardiac computed tomography (CT), and cardiac magnetic resonance imaging (MRI). While each modality has individual strengths and limitations, MRI is often considered the reference standard for the determination of both LVEF and RVEF based on its superior accuracy and reliability.

Despite significant data examining the accuracy of individual modalities to assess LVEF and RVEF compared with MRI, only one small study of 36 patients has compared the accuracy of LVEF using multiple modalities in the same patients and no study has provided a multimodality comparison of RVEF estimation techniques. We sought to utilize meta-analytic methods to determine the LVEF and RVEF pooled bias (mean weighted difference), limits of agreement (LOA), and correlation coefficient for each modality when compared with MRI.

Methods

We followed the PRISMA statement and systematically searched PUBMED for studies published from 1 January 1966 to 31 October 2014. We used the search terms and corresponding MeSH headings for ‘ejection fraction’ and ‘cardiac MRI’ limited to English language, adult human trials (full syntax in Appendix A). We then searched the references of all retrieved articles. In order for a study to be included in our analysis, it had to report Bland–Altman bias and LOA or correlation coefficient (r) for LVEF or RVEF by the modality in question when compared with MRI in adult humans. Studies not meeting these specific inclusion criteria were excluded.

Two investigators (C.A.P. and M.K.C.) independently abstracted data using a standardized extraction tool. Data included modality characteristics, study characteristics, patient characteristics, and the ‘outcome’ of Bland–Altman bias with LOA and correlation coefficient (r) for each study. Two investigators (C.A.P. and D.K.) independently assessed the quality of each study using the QUADAS-2 criteria. Disagreements were resolved by consensus.

We pooled the Bland–Altman biases and LOA and correlation coefficients using a random-effects model, and assessed for variance using the exact binomial method. Heterogeneity was assessed visually with Galbraith plots. We conducted a sensitivity analysis and meta-regression to assess the effects of study characteristics (such as mean ejection fraction). All statistics were performed with Stata v12.1 (College Station, TX, USA) using the metan commands. P-values were two-sided with an alpha value of 0.05. We assessed for publication bias using Begg’s test for a publication bias.

Results

Results of the literature search are presented in Figure 1. Ultimately, the search yielded 1531 citations, which after title and abstract review resulted in 345 studies. Of these, 139 were excluded for various reasons as shown in Figure 1, and 206 studies were included in the final meta-analysis. LVEF was reported in 174 studies, and 46 studies reported RVEF, 14 of which reported both RVEF and LVEF. Ultimately, there were 7047 patients in the LVEF group and 1730 patients in the RVEF group. Supplementary data online, Table S1 contains a comprehensive list of all included studies and each study’s associated data.

Baseline demographics of included patients were diverse, ranging from normal healthy adults to adults with congenital heart disease and severe cardiomyopathies. Patient characteristics such as age, gender, height, and weight were seldom reported in detail among original studies. The included studies were of moderate quality by the QUADAS-2 criteria: with a median and mode of 2 out of a possible 4 for each study.

Table 1: LVEF bias (mean weighted difference) and 95% LOA

<table>
<thead>
<tr>
<th>Modality</th>
<th>Bias (LOA)</th>
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<tbody>
<tr>
<td>CT</td>
<td>1.11% (−4.0 to 6.2)</td>
</tr>
<tr>
<td>IVC</td>
<td>−2.38% (−9.4 to 4.8)</td>
</tr>
<tr>
<td>3DE</td>
<td>0.71% (−4.9 to 6.3)</td>
</tr>
<tr>
<td>2DE</td>
<td>−0.57% (−13.3 to 12.1)</td>
</tr>
<tr>
<td>SPECT</td>
<td>3.03% (−6.2 to 12.2)</td>
</tr>
<tr>
<td>RNV</td>
<td>2.66% (−7.7 to 13.0)</td>
</tr>
</tbody>
</table>

2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiography; IVC, invasive cardiac cine ventriculography; CT, cardiac computed tomography; MRI, cardiac magnetic resonance imaging; RNV, radionuclide ventriculography; SPECT, cardiac single-photon emission computed tomography.

The mean weighted Bland–Altman difference (bias) for each modality when compared with the gold standard of cardiac MRI is listed in Table 1. CT and 3DE had the narrowest LOA with a median and mode of 2 of a possible 4 for each study. LVEF ranging from −4.0 to 6.2%, and 3DE overestimated LVEF by 0.71% with an LOA of −4.9 to 6.3%. Mean weighted biases and LOA are visually represented in Figure 2.

Left ventricular ejection fraction

The mean weighted Bland–Altman difference (bias) for each modality when compared with the gold standard of cardiac MRI is listed in Table 1. CT and 3DE had the narrowest LOA with a median and mode of 2 with cardiac MRI, CT overestimated LVEF by 1.11% with 95% LOA ranging from −4.0 to 6.2%, and 3DE overestimated LVEF by 0.71% with an LOA of −4.9 to 6.3%. Mean weighted biases and LOA are visually represented in Figure 2.

The pooled weighted correlation coefficients (Rho (r)) showed that all modalities correlate well with cardiac MRI, with the exception of 2DE (Table 2). 2DE had a statistically significant weaker correlation with MRI when compared with both the other modalities studied at
The mean weighted Bland–Altman difference (bias) for each modality for RVEF when compared with the gold standard of cardiac MRI is listed in Table 3. CT and 3DE performed well when compared with cardiac MRI with CT overestimating RVEF by 4.67% with 95% LOA ranging from −2.37 to 5.62%, and 3DE overestimating RVEF by 1.16% with an LOA of −0.59 to 2.92%. There was insufficient data to determine the pooled biases for the other modalities.

The pooled weighted correlation coefficients [Rho (r)] showed that CT, 3DE, and RNV correlate well with cardiac MRI, with RNV performing the best, numerically (Table 4). There were insufficient data to report on the correlation of 2DE, ICV, and SPECT with MRI for RVEF.

**Sensitivity analysis**

We performed a meta-regression to determine if lower ejection fractions resulted in poorer or better performance of one modality when
compared with another with respect to MRI, and found no statistically significant evidence of such an effect.

Discussion

There are several important findings from this meta-analysis performed from studies involving a large number of patients in whom measures of LVEF and RVEF using various modalities were assessed and compared with MRI. First, we determined that all techniques comparably estimated LVEF with a bias of <5%. Secondly, we demonstrated that there are small but significant differences in the variability in LVEF measurements when compared with MRI. For example, CT, 3DE, SPECT, and RNV had the highest correlation with LVEF by MRI, and CT and 3DE had the narrowest LOA. Conversely, 2DE had statistically significant weaker correlation for LVEF. For RVEF, CT and 3DE comparably estimate RVEF and have the most data to support their use.

Our analysis is consistent with a previously reported analysis that showed CT to be the most accurate in estimating LVEF when compared with MRI as a reference standard. Similarly, our analysis demonstrated that the LOA, and therefore variability in the measurement of LVEF, tended to be narrower with CT. This finding follows logically since one might expect the 3D tomographic dataset to have advantages for estimation of LVEF and RVEF relative to single-plane 2D echo estimation. LVEF estimated by 2D echo relies on geometric assumptions and a single-plane calculation of end diastolic volume and end systolic volume, thus introducing significant inaccuracy. Furthermore, our analysis adds comparison of MRI with 3DE, which demonstrated comparable performance to CT for the estimation of LVEF and RVEF. Our analysis also confirms results from smaller previous studies, demonstrating that the degree of over- and underestimation of LVEF between different modalities when compared with cardiac MRI is of questionable clinical significance (e.g. consistently <5% when compared with cardiac MRI).

The results of this analysis are clinically important, given the prognostic significance of LVEF. Furthermore, LVEF plays a pivotal role in the allocation of many interventions that reduce cardiovascular morbidity and mortality, such as implantable cardioverter defibrillator, cardiac resynchronization therapy, and medical therapies including angiotensin-converting-enzyme inhibitors, beta-blockers, and aldosterone antagonists, among many other patient-specific considerations. Finally, more precise LVEF and RVEF estimations have importance for sample size estimation of clinical research, indicating that studies with more reproducible technology such as MRI, 3DE, or CT will reduce cost through a smaller sample size relative to the comparatively less reliable 2D echo, which to date has otherwise been the mainstay of LVEF assessment for clinical trial work due to its widespread availability.

For RVEF, only CT and 3DE had adequate data to support analysis and therefore have the most data to support their use. CT and 3DE performed equivalently in assessing RVEF when compared with MRI, albeit this was data from only 46 studies.

Limitations

Our study has several limitations to be considered. The first limitation is the quality of studies available to complete this meta-analysis. Many studies did not report key patient characteristics in a manner that enabled meaningful stratification by risk factors and modality-specific parameters known to affect image quality (e.g. obesity, lung disease, and heart rate). Secondly, there was a wide variety of disease states represented in this study, ranging from normal patients and common conditions (e.g. hypertension and coronary artery disease) to adults with complex congenital heart disease. Thus, generalizability to specific populations may be limited. Nonetheless, meta-regression analysis across modalities found good accuracy at even lower ejection fractions, suggesting robust performance of included techniques across disease spectra. Additionally, a wide variety of techniques were employed across studies that are known to affect ejection fraction estimation, to include patient preparation manoeuvres, old vs. new hardware, and a variety of software and post-processing techniques (see ‘Modality Description’, Supplementary data online, Table S1). While included studies provide more modality- and technique-specific comparisons with cardiac MRI, our study provides the first large-scale comparison of existing literature in this area. Finally, conclusions about modality performance in RVEF assessment are limited by the scarcity of data, as only 46 studies were available for CT and 3DE in comparison with MRI.

Conclusion

In a meta-analysis of a large number of trials and patients comparing LVEF and RVEF as determined from multiple modalities to the gold standard of cardiac MRI, we determined that all studies comparatively estimated LVEF with a bias of <5%. CT, 3DE, SPECT, and RNV had the highest correlation and the 3D modalities, CT and 3DE had the narrowest LOA for LVEF. For RVEF, CT and 3DE comparably estimate RVEF and have the most data to support their use.

Supplementary data

Supplementary data are available at European Heart Journal – Cardiovascular Imaging online.

Conflict of interest: The views expressed in this article are those of the authors only and should not be construed to represent in any way...
Appendix A

Full syntax of literature search


Appendix B

References for Supplementary data online, Table S1.