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Cardiac Imaging to assess Left Ventricular Systolic Function in Atrial Fibrillation

Running title: Assessing systolic function in atrial fibrillation

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ABSTRACT

The validity and reproducibility of systolic function assessment in patients with atrial fibrillation (AF) using cardiac magnetic resonance (CMR), echocardiography, nuclear imaging and computed tomography (CT) is unknown. A prospectively-registered systematic review was performed, including 24 published studies with patients in AF at the time of imaging and reporting validity or reproducibility data on left ventricular systolic parameters (PROSPERO: CRD42018091674). Data extraction and risk of bias were performed by 2 investigators independently and synthesized qualitatively. In 3 CMR studies (40 AF patients), LVEF and stroke volume measurements correlated highly with catheter angiography ($r \geq 0.85$), and intra/inter-observer variability were low. From 3 nuclear studies (171 AF patients), there were no external validation assessments but intra/inter-observer and inter-session variability were low. In 18 echocardiography studies (2566 AF patients), 2 studies showed high external validity of global longitudinal strain (GLS) and tissue Doppler s' with angiography-derived dP/dt ($r \geq 0.88$). GLS and myocardial performance index were both associated with adverse cardiovascular events. Reproducibility of echocardiography was better when selecting an index beat (where two preceding RR intervals are similar) compared to averaging of consecutive beats. There were no studies relating to CT. Most studies were small and biased by selection of patients with good quality images, limiting clinical extrapolation of results. The validity of systolic function measurements in patients with AF remains unclear due to the paucity of good-quality data.

Keywords

Atrial fibrillation; systolic function; multi-modality imaging; validity

INTRODUCTION

Atrial fibrillation (AF) prevalence is expected to rise considerably over the next few decades.[1] To enable clinicians to provide appropriate therapy and improve prognosis, it is essential that systolic function can be accurately assessed.[2] Echocardiography, cardiovascular magnetic resonance imaging (CMR), computed tomography (CT), invasive angiography and nuclear scintigraphy are all used to assess systolic function. However, cardiac imaging in patients with AF is challenging due to R-R interval irregularity and/or elevated heart rate[3] which impact on validity and reproducibility, causing difficulties in acquiring diagnostic-quality images and interpretation of results.[4] The assumption that parameters used to quantify systolic dysfunction in patients with sinus rhythm have the same validity in AF may also be incorrect.[5,6] The aim of this systematic review was to determine if different modalities of systolic assessment have clinical value in patients with AF, to assist in the diagnosis of heart failure and guide optimal management for patients.

METHODS

All studies reporting validity or reproducibility data on left ventricular (LV) systolic function in AF patients were examined. There was no restriction on study design, however only human populations with AF at the time of imaging were included. Exclusion criteria were case reports, studies that were only published in abstract form, and those in a language other than English. All editorials, commentaries and informal reviews of other literature were also excluded. An online search was performed of PubMed, Embase and MEDLINE through the OVID library (inception to February 2019), including the broad terms “atrial fibrillation”, “angiography”, “computed tomography”, “cardiac magnetic resonance”, “nuclear imaging” and “echocardiography” using MESH headings and title/abstract searches, including syntax variations (Supplementary Table 1). We also conducted manual screening of relevant reviews and reference lists. The review was prospectively published on PROSPERO

(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=91674) and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

The primary outcomes of interest were the validity and reproducibility of LV systolic assessment in AF patients using different imaging modalities. For echocardiography, these included left ventricular ejection fraction (LVEF) (measured either by Simpson's biplane method or three-dimensional [3D] volume assessment), fractional shortening, stroke volume derived from left ventricular outflow tract pulsed wave Doppler, tissue Doppler velocities, pre-ejection period derived myocardial performance index (MPI), peak longitudinal systolic strain and global longitudinal strain [GLS]. For CMR, this included volume-derived LVEF, GLS using either feature tracking or myocardial tagging, and stroke volume derived from flow mapping in the aortic root. For nuclear medicine, this included measurements of LVEF derived from radionuclide equilibrium angiography, gated single photon positron emission tomography (SPECT) and gated positron emission tomography. We extracted data systematically using a standardised extraction form to ascertain: (1) validity against other imaging modalities (external validation); (2) association with clinical or surrogate endpoints; (3) comparison within an imaging modality (internal validity); and (4) measurements of intra- and inter-operator reproducibility.

Two investigators independently assessed inclusion at full text level and extracted relevant variables (KB and KO). Disagreements were resolved by consensus review and additional independent adjudication (DK). Variables of interest for validity were strength of association using correlation (r) and intra-class correlation coefficient (ICC), and agreement using Bland and Altman analysis. For association with clinical parameters, hazard ratios, chi-squared tests, area under the curve and Kaplan-Meier analysis were also included. Variables of interest for reproducibility were agreement using Bland and Altman analysis and mean difference, association measured using correlation coefficients, linear regression (r^2) and ICC, and variability measured using percentage change, coefficient of variation and repeatability coefficient. Study quality was assessed using

Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).[7] Risk of bias was similarly assessed by 2 investigators independently, covering bias and applicability on the level of patient selection, the index test, reference standard and study flow and timing (Supplementary Table 2).

Baseline demographics were pooled from all studies providing suitable data (including variance where applicable), and are summarized as a weighted mean according to sample size. Outcomes were synthesized qualitatively. Meta-analysis of comparative data between AF and sinus rhythm was not possible due to the limited studies available and a lack of published data on the variance of outcome measures.

RESULTS

The search strategy identified a total of 7382 papers of which 7058 were excluded mainly due to a lack of relevance to the research question. After the full text was screened, a further 310 studies were excluded leaving a total of 24 studies which were then sorted into each imaging modality (**Figure 1**). Overall risk of bias is presented in **Figure 2**, highlighting concern about patient selection bias. Results are presented by imaging modality in the text below, and are categorised in the tables according to external validity (**Table 1**), internal validity (**Table 2**), association with clinical or surrogate endpoints (**Table 3**), and reproducibility (**Table 4**). The full list of included studies with population details and methods is presented in Supplemental Table 3.

Cardiac Magnetic Resonance Imaging

Three CMR studies were included, assessing a total of 40 AF patients with breath-hold cines using steady-state free precession imaging (SSFP) of the LV to calculate stroke volume or LVEF. We identified no studies assessing the reproducibility or validity of phase mapping or strain imaging in patients with AF at the time of imaging. The method of patient selection, and flow and timing of data obtained was unclear for these studies; hence the risk of bias was unclear.

One study externally validated CMR parameters of LVEF and stroke volume against invasive catheter angiography in 13 AF patients; 3 of these patients were excluded due to frequent ventricular ectopy, the need to void, or data corruption.[8] Of the remaining patients, "several" required hand-drawn endocardial borders rather than the semi-automated process due to insufficient contrast with the blood pool (this may have led to differential risk of bias compared to 12 patients in sinus rhythm). CMR-derived LVEF was shown to correlate strongly with left ventriculography (r=0.85), with a mean difference of 0% (SD 0.08) and no excess variability compared to sinus rhythm patients (p=0.37). Similar results were seen for CMR-derived stroke volume using both flow-based and volume-based measurements. Another study internally validated LVEF by comparing compressed sensing and parallel imaging (SPARSE-SENSE) with conventional SSFP in 20 patients with AF; they identified a strong correlation between techniques (ICC=0.97, 95% CI 0.93-0.99; p=0.14), but heart rate at the time of assessment was not stated.[9]

Three studies examined the reproducibility of systolic parameters using CMR. LVEF inter-observer reproducibility in 10 patients was better using CMR as compared to angiography (SE 8% versus 14%), with similar results for stroke volume (SE 9mL versus 24mL), but again no comment on heart rate.[8] In 20 patients there was no relevant difference in intra/inter-observer reproducibility between SSFP and real-time SPARSE-SENSE. In 10 patients with permanent AF and a mean heart rate of 82 bpm (range 57-109), intra-observer reproducibility was good (R^2=0.97), repeatability coefficient was 3.8 and Bland and Altman bias was -1.9%. Inter-study reproducibility was also good (R^2=0.99), with repeatability coefficient 1.3 and Bland and Altman bias of 0.5%.[10]

Nuclear Imaging

We identified no studies in which systolic parameters were externally validated or correlated with other clinical parameters in patients with AF. Three nuclear imaging studies were included that addressed either internal validity (i.e. against other nuclear imaging) or reproducibility, with a total of 171 AF patients. The method of patient selection, and degree of blinding to the index and reference test was not stated clearly in these studies, making the risk of bias unclear.

AF gating errors significantly affected the measurement of wall thickening (60% ± 299%) and myocardial perfusion (76% ± 352%) in a study of 35 AF patients with suspected coronary artery disease.[11] Gated SPECT in this study had a strong correlation with equilibrium radionuclide angiocardiography (r=0.89; p<0.0001), however LVEF measured by SPECT was consistently lower by 3-4%. In a study of 20 AF patients, cycle length windowing as a way to overcome the variable rhythm in AF showed similar LVEF values compared to non-windowed parameters (p=0.16), with strong correlation between the 2 methods (r=0.97).[12]

The reproducibility of measuring volumes and LVEF was assessed in 115 patients with AF using myocardial perfusion gated SPECT, demonstrating low intra/inter-observer variability (0.22% and 0.47%), and low variation between two consecutively taken studies (ICC=0.95).[13]

Echocardiography

Eighteen echocardiography studies were included, with a total of 2566 AF patients. The method of patient selection for most echocardiography studies incurred a high risk of bias, due to the exclusion of patients with poor imaging windows.

Two studies (total 64 patients) externally validated echocardiographic systolic parameters against dP/dt derived from invasive angiography, with GLS found to have a strong correlation with averaged dP/dt (r=0.94; p<0.001).[14] The tissue Doppler parameter s' was also shown to correlate strongly with dP/dt (r=0.88; p<0.0001).[15] Eight studies compared echocardiographic indices of systolic function with clinical parameters or surrogate biomarkers. [16-23] In 1293 AF patients who had suffered a myocardial infarction, lower LVEF (estimated using an echocardiographic wall motion score) was associated with an increase in the risk of 30-day mortality (8% for patients with LVEF >50%, 10% for LVEF 36-50%, 24% for LVEF 26-35% and 40% for LVEF <25%).[19] However, lower LVEF did not appear to predict long-term mortality in AF patients. Lower GLS was associated with adverse cardiovascular events in two studies of 196 and 204 AF patients[17, 20], with similar results seen with global circumferential strain and when GLS was corrected for R to R

interval.[21] MPI was associated with cardiovascular events in 196 patients (hazard ratio 1.10 per 0.1 unit increase; 95% CI 1.03-1.18; p= 0.004).[22] In 104 patients with AF, Simpson's biplane LVEF correlated only weakly with B-type natriuretic peptide (r=-0.25; p=0.07).[16] Similar results were seen for atrial natriuretic peptide in 67 patients using Teichholz-derived LVEF (r=-0.42, p=0.01).[18]

Four studies performed internal validation with other echocardiographic parameters (**Table 2**).[24-27] Eight studies assessed reproducibility, but there have been no echocardiographic studies comparing reproducibility directly with other imaging modalities. A variety of small studies have demonstrated low levels of intra and inter-observer variability for LVEF, GLS and MPI when reassessing systolic function in AF patients using echocardiography (**Table 4**). 3D measurement of LVEF was shown to be more reproducible when calculated using a single-beat analysis compared to 4-beat averaging (intra-observer variability 4.8% versus 8.3%; inter-observer 5.6% versus 18%).[28] An index beat approach, whereby measurement is made following two RR intervals of similar length resulted in lower intra and inter-observer variability compared to conventional averaging of consecutive beats.[14, 17, 29]

Computed Tomography

There were no studies assessing validity, association with clinical endpoints, or reproducibility of systolic function in patients with AF using computed tomography.

DISCUSSION

This is the first systematic review of the validity and reproducibility of systolic measurements made using standard cardiovascular imaging modalities for patients in AF at the time of assessment. Adequate data on external validation against clinical events or surrogate outcomes is severely lacking, meaning that the clinical utility of systolic function assessment in the context of AF is uncertain particularly for CMR, nuclear and CT imaging modalities where there were no validation studies with clinical outcome. Comparison of validity and reproducibility between different imaging modalities is also extremely limited; hence measurements of systolic LV function

commonly used in patients with AF cannot reliably be interchanged. Assessment of systolic function in patients with AF is performed in every cardiac centre globally, and yet there is limited scientific data on measurement quality or validity.

Most of the studies included in this systematic review addressed echocardiography, with limited examination of other modalities. Even within echocardiography, there is a clear lack of external validation. CMR is generally considered the gold-standard method for assessing systolic function in routine practice[30], however in AF patients we do not have sufficient data on direct comparison with high-fidelity invasive pressure assessment. dP/dt is only a good marker for end-systolic elastance (the true gold standard for assessing LV contractility) when arterial pulse pressure variation is low[31], which is unlikely in those with AF. There have been no studies externally validating LVEF in AF patients, which is a concern given that this measurement is used as key parameter to guide patient management.[2] In heart failure patients with sinus rhythm, LVEF is closely related to clinical outcomes, with each 5% lower LVEF increasing the risk of all-cause mortality by 24% (n=14261 patients; 95% CI 21-28%; p<0.0001).[6] However in patients with AF, the relationship of LVEF with clinical outcomes is less substantial, with a 9% increase in mortality per 5% lower LVEF (95% CI 3-15%; p=0.002), likely reflecting the higher variability in AF patients.[6] LVEF thresholds guide management decisions for patients.[2] This highlights the importance of understanding the accuracy and validity of systolic function assessment in patients with AF; unfortunately our review suggests that this is far from secure. GLS has been shown to provide prognostic information and so may be reliable method of assessing systolic function in patients with AF, however these studies were all highly biased for only selecting patients with adequate echocardiographic windows.[17, 20, 21]

The reproducibility of LVEF appears to be reasonable in these AF studies, with low levels of intra and inter-observer variability. However, the patients included were selected for good quality imaging[32, 33] and reproducibility assessment did not include the full range of testing (for example, repeatability and reliability).[4] These studies are unlikely to represent the AF population

scanned in routine practice, as AF patients usually have multiple co-morbidities such as obesity and airways disease limiting image quality. Moreover, the same images were often re-analysed, rather than the study itself repeated, thereby excluding the inter-session variability in measurements that would be expected in clinical practice. For calculation of parameters, guidelines recommend averaging 5-10 consecutive beats in patients with AF[34, 35], which is time-consuming and is often not completed in routine care.[22] In contrast, the use of an index beat has been shown to be reproducible and could have advantages over averaging beats in AF.[14, 20, 28, 29]

Finally, in all studies where heart rate was reported, values were within a well-controlled range of 60-90 beats per minute. There have been no studies assessing the validity or reproducibility of systolic parameters when heart rates are outside this range. It is generally considered that measurements taken in patients with a ventricular rate >100 bpm are unreliable[36], however there have been no studies to allow us to make an evidence-based recommendation.

In conclusion, there is a clear need for external validation of systolic measurements in patients with AF and also inter-operator/inter-session studies to better assess reproducibility. Data on the validity of measurements in CMR, nuclear imaging and CT were extremely limited, making it difficult to draw any conclusions. A major limitation of the reproducibility studies was the lack of blinding of observers, leading to an uncertain risk of bias for work flow, index and reference values. Moving forward, we urgently need prospective, blinded comparison studies in AF patients, with imaging not restricted to participants with high quality images. Only with this knowledge can we be certain that measurements derived from cardiac imaging truly reflect underlying systolic function in patients with AF.

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Conflicts

All authors have completed the ICMJE uniform disclosure form and declare:

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FIGURE LEGENDS

Figure 1. Systematic review flowchart.

Flowchart showing the number of papers included and excluded at each stage of the screening process.

AF= atrial fibrillation; CT= computed tomography; MRI= magnetic resonance imaging.

Figure 2. Risk of bias overall studies according to QUADAS-2 assessment

Bar chart (left panel) to display the proportion of studies with low, high or unclear bias according to the categories: work flow, reference test, index test and patient selection. Bar chart (right panel) to display the proportion of studies with low, high or unclear concerns of applicability according to the categories: reference test, index test and patient selection.

Figure 3. Summary of findings from each imaging modality

CMR image of a mid-short axis slice acquired by SSFP retrospective gating (top left panel); TTE three-dimensional imaging of the left ventricle in the apical window (bottom left panel); radionuclide ventriculography imaging with left ventricular contours (top right panel); cardiac CT image of the left ventricle (bottom right panel).

CMR= cardiac magnetic resonance; SSFP= standard steady state free precession; TTE= transthoracic echocardiography; CCT= cardiac computed tomography