Is echocardiography valid and reproducible in patients with atrial fibrillation? A systematic review

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Received 28 November 2016; editorial decision 25 January 2017; accepted 10 February 2017

Aims

Echocardiography is vital in the routine assessment and management of atrial fibrillation (AF). We performed a systematic review of the validity and reproducibility of echocardiographic left ventricular systolic and diastolic function in AF, and optimal acquisition methods.

Methods and results

Online databases were searched for studies in patients with AF at the time of echocardiography (1960 to August 2015), prospectively registered with PROSPERO (CRD42015025297). The systematic review included 32 studies from 3 066 search results (1 968 patients with AF). Average age was 67 years, 33% were women, mean LVEF 53% (±10%), and average E/e’ 11.7 (±2.7). Data on the validity and reproducibility of systolic indices were extremely limited. In contrast, diastolic parameters demonstrated correlation with invasive filling pressure and adequate reproducibility: E/e’ (n = 444) r = 0.47 to 0.79; IVRT (n = 177) r = −0.70 to −0.95; E/Vp’ (n = 55) r = 0.63 and 0.65; pulmonary vein diastolic flow (n = 67) r = −0.80 and −0.91. Elevated E/e’ (>15) was associated with functional capacity, quality of life, and impaired prognosis. For optimal acquisition in AF patients, cardiac cycles with controlled heart rate (<100 beats/min) and similar preceding and pre-preceding RR intervals are required. Cardiac cycle length and equivalence were more important than the number of beats averaged.

Conclusion

With careful selection of appropriate cardiac cycles, echocardiography is a valid tool to identify diastolic dysfunction in AF, and E/e’ is an independent marker of clinical status and adverse prognosis. However, data on systolic function was extremely limited and requires further prospective study and assessment of variability in clinical practice.

Keywords

Atrial fibrillation • Echocardiography • Reproducibility • Ejection fraction • Heart failure • Diastolic • Systematic review

Introduction

Atrial fibrillation (AF) is an increasingly common heart rhythm disturbance that leads to frequent hospital admissions, heart failure, stroke, and higher mortality.1 There is a close relationship between AF and heart failure, with numerous risk factors common to both conditions, and shared pathophysiology in patients with both reduced2 and preserved3 left ventricular ejection fraction (LVEF). Depending on the type of AF, the rate of prevalent heart failure is between 33% and 56%; hence clinicians treating patients with AF need reliable information on both systolic and diastolic left ventricular (LV) function. Echocardiography is the primary tool used in clinical
What’s new?

- The new 2016 ESC Guidelines on AF recommend echocardiography in all AF patients to guide management (I C).
- In this systematic review, data on the validity and reproducibility of systolic indices in AF patients were extremely limited; the best measure of systolic function and acquisition method in AF are priorities for future research.
- Diastolic parameters in AF have been validated against invasive filling pressure with adequate reproducibility. Elevated E/e’ (>15) is also associated with functional capacity, quality of life, and impaired prognosis.
- Measurement of systolic and diastolic function in AF is optimized when the two preceding cardiac cycles have similar RR-intervals and the heart rate is controlled (<100 beats/min).

practice and provides vital guidance to determine appropriate use of anticoagulation, rate-control therapy, and rhythm-control strategies, as well as important information on co-existing or precipitating pathology and prognostic data. All of these important clinical decisions require echocardiographic measures that are valid and reproducible, regardless of cardiac rhythm.

The loss of synchronized atrial contraction and altered left atrial pressure is likely to affect the reproducibility of echocardiographic measurements in AF. Factors that have been implicated include the ratio of preceding to pre-preceding cycle length and heart rate during image acquisition. Both of these influence the volume of ejection and consequently the results of the most commonly-used measurements of LV function, particularly where these are taken over a number of cardiac cycles. Joint guidelines published by the American Society of Echocardiography and the European Association of Cardiovascular Imaging suggest a minimum of five beats in AF patients, although this is based on consensus opinion. For diastolic function, the British Society of Echocardiography recommends averaging over 5–10 beats during cycle lengths equivalent to a heart rate between 60–80 beats/min.

We performed a systematic and focused review of published literature on the use of echocardiography for determination of systolic and diastolic LV function in patients with AF. Our main objectives were to assess the validity of echocardiographic measures whilst in AF, both against other modalities and clinical outcomes, and the reproducibility of these parameters. A further objective was to appraise the acquisition of images. This includes the optimal number of repeated measurements and cardiac cycle lengths that would reduce variability of systolic and diastolic evaluation and allow confidence in the echocardiographic diagnosis of systolic or diastolic dysfunction in AF.

Methods

Eligibility criteria and search strategy

All studies reporting validity or reproducibility data on LV systolic or diastolic function in AF patients were examined. There was no restriction on study design, however only adult populations with AF at the time of echocardiography were considered. Exclusion criteria included case reports, animal studies and studies that were only published in abstract form or in a language other than English. All editorials, commentaries and informal reviews of other literature were also excluded, as were studies only assessing left atrial size or function. An online search was performed of PubMed and the Cochrane library (inception to December 2014, and then extended to August 2015), including the broad terms ‘atrial fibrillation’ and ‘echocardiography’ using MESH headings and title/abstract searches, including syntax variations. We also conducted manual screening of relevant reviews and reference lists. The systematic review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and prospectively registered with the PROSPERO database of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015025297).

Outcomes

The primary outcomes of interest were echocardiographic measures of LV systolic and diastolic function. For systolic function, these included LVEF using biplane Simpson’s method or 3D volume assessment and measurement of strain (peak longitudinal systolic strain [PLSS] and global longitudinal strain [GLS]). For diastolic function, we included assessment of isovolumic relaxation time (IVRT), mitral E-wave deceleration time, the ratio of mitral peak E velocity to tissue Doppler early diastolic velocity e’ (E/e’), pulmonary venous (PV) flow diastolic deceleration time (PVd-DT), and the ratio of mitral peak E velocity to the velocity of diastolic flow propagation measured with colour Doppler M-mode (E/VTp). For all parameters, we extracted data on validity against other modalities (for example, pulmonary capillary wedge pressure [PCWP] on right heart catheterization) and estimates of intra and inter-operator reproducibility. We also noted the method by which studies collected data, including the number of repeated measures and cardiac cycle lengths. A secondary outcome was to record average values of echocardiographic measures in AF, for comparison with published norms in patients with sinus rhythm.

Data collection and quality assessment

Data on validity (against other modalities and any relevant clinical associations) and reproducibility (both intra- and inter-observer variability) were extracted by three investigators independently (MM, ES, and DK), and tabulated in a standardized data-extraction form. Study quality was assessed using the Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS), which addresses selection bias, exposure measurement, blinding, the completeness of outcome data, and selectivity of reporting. Risk of bias was assessed by two investigators independently (MM and ES) and discrepancies resolved by group discussion and additional adjudication (DK).

Data synthesis and statistical analysis

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. Analyses were performed on Stata Version 14.1 (StataCorp LP, Texas).

Results

The search strategy identified a total of 3066 records of which 2945 were excluded, primarily due to lack of relevance to echocardiography in AF, and a further 89 excluded after full text review (Figure 1).
Thirty-two observational studies were included in the final review,8–39 the majority of which were single-centre studies. Table 1 highlights the populations examined and the key findings relating to patients with AF. There was marked heterogeneity in the type of AF (paroxysmal, persistent, or permanent), heart failure status, LVEF and clinical demographics. The weighted-average age was 66.9 years and a third were women (Table 2). Overall, studies recorded a mean LVEF of 52.5% and average E/e′ of 11.7 in AF. Heart rate was usually below 80 beats/min, with a minority of studies excluding patients above a specific heart rate target (typically >100 beats/min). Many studies excluded patients with AF due to valvular heart disease. Only four studies enrolled 100 or more patients, and there were frequent references to selecting participants with adequate quality echocardiographic images. As a result, the risk of bias for selection and blinding were universally high, although in other domains, the risk of bias was more variable (see Supplementary material online, Table S1).

**Systolic function: validity and reproducibility**

Data for the validity of systolic function indices in patients with AF were extremely limited. We found no external validation studies (for example, comparing results with other modalities such as cardiac magnetic resonance or nuclear imaging). There were however examples of within-study or internal validation (such as correlation of new 3D techniques with conventional biplane Simpsons, or strain with LVEF).9,33 With respect to clinical outcomes, one study showed that LV systolic parameters were unrelated to exercise capacity in 73 stable AF patients.17 However, in a study of 196 patients with persistent AF, baseline GLS was independently associated with a composite of cardiovascular death, non-fatal stroke and heart failure hospitalization after 21 (±10) months follow-up.32 This relationship persisted in multivariate analysis (hazard ratio 1.12, 95% CI 1.02–1.23, P = 0.014), whereas LVEF and other measures of systolic function were not independently significant. The optimal, post-hoc defined GLS cut-off for predicting event-free survival was −12.5%, and this incrementally added to clinical predictors of adverse outcome.32

Reproducibility of systolic function indices are summarized in Table 3. A wide array of study and acquisition methods made data synthesis unfeasible, however reproducibility was reasonable in AF patients using single-beat methods.19,29,31,32,39 One study examining AF patients with irregularity on their electrocardiogram found that to achieve similar variability for cardiac output in AF as with sinus rhythm, three times the number of beats were required (13 vs. 4 beats, respectively).12 In contrast, although there was higher inter-observer variability for 3D-LVEF using conventional 4-beat acquisition in AF compared to sinus rhythm (17.9% vs. 3.9%, respectively), when using single-beat acquisition, reproducibility was similar regardless of heart rhythm (5.6% in AF, vs. 4.5% in sinus rhythm).29

**Diastolic function: validity and reproducibility**

Considerably more data were available for the use of diastolic parameters in AF (Table 4). Twenty studies provided correlations with invasive PCWP on right heart catheterization for a range of diastolic indices. IVRT was assessed in four studies (n = 177) and inverse correlations with PCWP were all highly statistically significant, ranging from −0.70 to −0.95.11,22,34,35 Seven studies examined mitral deceleration time (n = 324), of which 2 found no correlation with PCWP27,30 and 5 identified moderate inverse correlation.10,21,22,34,35 All 5 studies of E/e′ (n = 444) showed significant association with PCWP, ranging from 0.47 to 0.79, and including e′ derived from both septal and lateral positions.15,20,27,30,36 Using a dual Doppler method, the combination of E/e′ and the time between E and e′ (cut-points at >14.6 and >34 ms, respectively), improved the sensitivity and specificity for predicting elevated PCWP vs. either alone.36 Compared to those in sinus rhythm, AF patients demonstrated a similar correlation with PCWP for the ratio of IVRT to time between E and e′ in patients with mitral valve disease.11 E/e′ and the deceleration time of PV diastolic flow were each assessed in 2 studies (n = 55 and n = 67, respectively) and both parameters showed a high degree of correlation with PCWP.10,21,22,24 Diastolic PV flow was better than mitral indices for estimating PCWP in one study of 35 AF patients.10

In regard to clinical outcomes, a retrospective analysis of 230 AF patients identified that septal E/e′ >15 was independently associated with mortality during follow-up of 245 (± 200) days, both in patients with impaired and preserved LVEF.23 Deceleration time <150 ms was associated with mortality during follow-up of 25 (± 11) months in AF patients with LVEF <40% who had been hospitalized for heart failure, with a similar impact in AF patients (n = 40) as those with sinus rhythm (n = 100).25 Diastolic indices, including E/e′ and E/e′/Vp, have also been shown to correlate with B-type natriuretic peptide (BNP), a biomarker strongly associated with adverse prognosis.15,25 E/e′ was the only echocardiographic variable of LV function related to exercise capacity in 73 patients with AF (multivariate adjusted coefficient β = −0.12; P = 0.032).17 The same group also showed in one of the only multicentre studies that septal E/e′ was associated with prior ischaemic stroke in 330 AF patients with LVEF >40% (adjusted odds ratio 1.21, 95% CI 1.08–1.37; P = 0.002), unlike clinical and
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3D, Three-dimensional; AF, atrial fibrillation; BNP, B-type natriuretic peptide; IVRT, isovolumic relaxation time; LV, left ventricular; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; PV, pulmonary vein.
Acquisition: cycle length and cycle repeats

The irregular RR interval in AF has led to concern about the reliability of both systolic and diastolic measures, and there is clinical uncertainty about the number of repeated measures required and optimal cycle length. Historical data have shown that the RR interval affects LVEF in AF patients, more so than in sinus rhythm. More recent studies have confirmed that the cycle length of preceding RR intervals in AF is strongly related to stroke volume. LV ejection velocity is lower when pre-preceding RR intervals are longer, and differences in systolic performance are minimized when the preceding and pre-preceding RR interval lengths are equivalent. Beating-to-beat variability in stroke volume increases as heart rate increases in AF patients, and the effect of preceding and pre-preceding RR intervals on stroke volume is most pronounced at higher heart rates.

With regard to the number of repeated measurements required, when preceding and pre-preceding RR interval lengths are equivalent (<60 ms difference), measurement of PLSS in patients with persistent or permanent AF was similar using a single index-beat, as compared to averaging 15 cardiac cycles (r = 0.97, P < 0.001). In another study, index-beat assessment gave similar values to 10-s averages for myocardial strain and strain rate (r = 0.94, P < 0.001). The benefit of averaging a number of beats with similar preceding and pre-preceding RR intervals and with cycle lengths of 500 ms or greater was confirmed in two further studies. Using 3D volume datasets, a single-beat measurement in AF had lower variability than conventional 4-beat acquisition, although whether a single-beat analysis has the same association with clinical outcomes is currently unknown. For diastolic function, retest variability of E/e’ was similar over 10 or 50 cardiac cycles in AF patients with preserved LVEF. In another study of post-operative AF patients, the correlation of E/e’ to PCWP was no different when sampling over 10 beats or in a single cycle with the longest RR interval (r = 0.47 and 0.44, respectively).

These results suggest that choosing appropriate cardiac cycles with similar RR interval is more important than the absolute number of cycles measured (Figure 2). Of clinical importance, Nagueh et al. found less Doppler variability in patients at higher LV filling pressure, suggesting that measurement error might actually be reduced in those patients at the highest risk of adverse events.

Discussion

The main findings of this systematic review were that diastolic indices, in particular E/e’, were valid and reproducible in patients with AF, whereas data for systolic parameters were extremely limited. We also identified consensus amongst numerous studies that the optimal acquisition of echocardiography in AF patients occurred when preceding and pre-preceding cycle lengths are equivalent, rather than according to the number of repeated measurements taken. These
findings have important clinical impact, dispelling preconceptions about the utility of diastolic variables, highlighting key areas in need of further prospective study, and improving the diagnostic value of echocardiography in patients with AF (Figure 3).

Echocardiography is a vital part of the assessment of AF patients, and is now recommend in all AF patients to guide management (class I, level of evidence C). Numerous narrative reviews have been published concerning both systolic and diastolic function, however, this is the first systematic assessment of the validity and reproducibility of measurements. Echocardiography is an important component of initial management and is cost-effective for newly diagnosed patients with AF. Knowledge about the type of heart failure in AF

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<th>Validity and reproducibility of diastolic echocardiographic measures in AF</th>
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<td><strong>Parameter/Study</strong></td>
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<td><strong>Isovolumic relaxation time (IVRT):</strong></td>
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<td><strong>Mitral E wave deceleration time:</strong></td>
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<td><strong>Ratio of mitral peak E velocity and tissue Doppler e’ (E/e’):</strong></td>
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<td>Wada, 2012</td>
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<td><strong>Ratio of mitral peak E velocity and velocity of diastolic flow propagation (E/Vp):</strong></td>
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<td><strong>Pulmonary venous flow diastolic wave deceleration time (PVD-DT):</strong></td>
<td></td>
</tr>
<tr>
<td>Chirillo, 1997</td>
<td>35</td>
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<tr>
<td>Matsukida, 2001</td>
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</table>

Retest variability typically expressed as the mean percentage error.

1IVRT as a ratio to the difference between onset time of mitral E and annulus e’ velocities.
2N= 7 for reproducibility data.
3Combined reproducibility assessment for all Doppler variables.
4N= 10 for reproducibility data.
5N= 6 for reproducibility data.
6N= 40 for reproducibility data; based on a composite of IVRT, deceleration rate and systolic fraction.
7Fractional shortening 29% (SD 4%).
8LVEF, left ventricular ejection fraction.
9P<0.05.
10P<0.01.
11P<0.001.
Figure 2. Example of optimal acquisition (index beat method). In order to achieve the most valid and reproducible measurement in atrial fibrillation, parameters should be acquired where the two preceding cardiac cycles have similar RR-intervals and preferably where the equivalent heart rate is < 100 beats/min (panel A). This method can also be applied to assessment of function; averaging individual index beats is preferable to averaging across sequential cardiac cycles (panel B).

Figure 3. Summary of findings for echocardiography in AF. AF, atrial fibrillation; E/e’, ratio of mitral peak E velocity and tissue Doppler early diastolic filling e’; E/Vp, ratio of mitral peak E velocity and the velocity of diastolic flow propagation; IVRT, isovolumic relaxation time; PCWP, pulmonary capillary wedge pressure; PVd-DT, pulmonary venous diastolic flow deceleration time.
cycles). However, it is unclear if this has any advantage over prop-
tween operators (7.1% vs. 13.4% using conventional analysis over 10
and in one study conferred a smaller amount of variability in E/e’ be-
appears to offer better validation vs. invasive PCWP (see
where successive beats are likely to vary. The dual Doppler method
tical advantages to this process in reducing error, particularly in AF
single-beat analysis of E/e’ (dual Doppler method). There are theor-
sessment of both E and e’ are now available in order to provide a
accurately identify LV dysfunction in AF patients. Simultaneous as-
length, particularly in respect to the RR intervals preceding measure-
have shown that stroke volume and LVEF do vary according to cycle
10
sions are reliable in AF, despite the irregular ejection and rate. We
reduced LVEF (p value for interaction = 0.036). Further prospective
have excluded or only enrolled those with heart failure, this was
similar to the RealiseAF Global Registry (LVEF 54.3% in persistent
and 53.3% in permanent AF).50 E/e’ values were consistently higher
seen in 103 healthy volunteers (lateral E/e’ 6.2 ± 1.8 in age-range
60-69 years) but similar to 100 sinus rhythm patients undergoing
coronary angiography56 and 951 sinus rhythm patients with isolated
diastolic dysfunction and e’/a’ <1.47 However, even though average
estimates are likely to be higher in AF patients (with associated comorbidities)
than sinus rhythm, the cut-off value of E/e’ >15 was still a good marker of adverse events and functional capacity in AF.
Validation of E/e’ against invasive filling pressure was reasonable in
AF, and similar to correlation values published in sinus rhythm. For
sinus rhythm, this includes lateral E/e’ r= 0.51 in 100 patients, lateral
E/e’ r= 0.86 in 100 patients, and septal E/e’ r= 0.46 in 60 echocardi-
gram studies in 15 patients.46,48,49 However, a recent systematic re-
view of E/e’ in sinus rhythm identified concerns over reliability of this
parameter to estimate LV filling pressure.50

In all cases, there is the assumption that echocardiographic param-
eters are reliable in AF, despite the irregular ejection and rate. We
have shown that stroke volume and LVEF do vary according to cycle
length, particularly in respect to the RR intervals preceding measure-
ment. In contrast to sinus rhythm, echocardiographers need to care-
fully appraise how and when to acquire measurements in order to
accurately identify LV dysfunction in AF patients. Simultaneous as-
essment of both E and e’ are now available in order to provide a
single-beat analysis of E/e’ (dual Doppler method). There are theor-
etical advantages to this process in reducing error; particularly in AF
where successive beats are likely to vary. The dual Doppler method
appears to offer better validation vs. invasive PCWP (see Table 4),
and in one study conferred a smaller amount of variability in E/e’ be-
tween operators (7.1% vs. 13.4% using conventional analysis over 10
cycles). However, it is unclear if this has any advantage over prop-
ery acquired index-beat assessment, and availability in clinical prac-
tice is currently limited. Whereas a properly acquired index-beat assessment approach, based on our data, should achieve good levels of validity and reproducibility for diastolic indices, the data on systolic parameters is clearly inadequate. It is unclear which measure of sys-
tolic function is best for patients who are scanned whilst in AF, and
this should be a priority for future research. Although global strain at
a low cut-off was associated with outcomes in one of the studies re-
viewed, more recent data suggests that the association of strain
with mortality is attenuated in patients with AF and heart failure with
reduced LVEF (p value for interaction = 0.036).51 Further prospective
studies, either in the context of controlled trials or in routine clin-
cal practice, are urgently needed to support the large volume of
echocardiograms performed in patients with AF. As clinicians, we
also need to know the minimum number of index beats required to
maintain equivalence but reduce the time required for scanning, and
for confirmation of reproducibility at different heart rates and grades
of systolic and diastolic LV dysfunction.

Study limitations
There are numerous limitations to our review, most notably the risk
of bias, particularly selection and blinding bias, as patients were often
selected on the basis of echocardiogram quality. However, this is no
different to studies in sinus rhythm. There are likely to be other stud-
ies assessing the reproducibility of echo parameters in AF, missed by
our systematic search if reproducibility was not listed as a major out-
come. We were unable to perform meta-analysis, not only because of
the lack of published standard deviations for validation and repro-
ducibility measures, but also the heterogeneity of populations as-
essed. Although most studies made reference to ‘chronic AF’, the
duration and type of AF was often not disclosed. Most of the studies
excluded valve disease (with differing definitions) and there was lim-
ited data above a heart rate of 100 beats/min. Finally, considering the
importance of diagnosing heart failure in patients with AF, and how
common these conditions are in clinical practice, the relatively small
number of studies identified in this systematic review is a surprising
limitation, and one that requires further attention.

Conclusions
In selected patients with atrial fibrillation, diastolic echocardiog-
graphic parameters have been validated against invasive filling pres-
sure, and E/e’ is an independent marker of functional impairment
and adverse prognosis. Averaging single-beat assessments are re-
producible and should be acquired in cycles with similar preceding
length and controlled heart rate. However, data on the validity and
reproducibility of systolic indices are extremely limited. Considering
the importance of heart failure and assessment of systolic function
in AF, further assessment of variability in routine clinical practice is
urgently needed.

Supplementary material
Supplementary material is available at Europace online.

Conflict of interest: All authors have completed the ICMJE conflict
of interest statement and report no conflicts. DK discloses non-
financial support from Daichi Sankyo, research grants from Menarini
and lecture fees from AtriCure, all outside the submitted work; and
Lead for the Beta-blockers in Heart Failure Collaborative Group (BB-
meta-HF) and the RAtel control Therapy Evaluation in Atrial
Fibrilliation (RATE-AF) trial. MM, ES and RS have no disclosures to re-
port. BAP disclose research support and honoraria from GE
Healthcare and Hitachi-Aloka, all outside the submitted work.

Funding
DK is supported by a National Institute of Health Research (NIHR)
Career Development Fellowship (CDF-2015-08-074). The opinions ex-
pressed in this paper are those of the authors and do not represent the
NIHR or the UK Department of Health.
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