Multimodality Cardiac Imaging for the Assessment of Left Atrial Function and the Association With Atrial Arrhythmias

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Abstract—Several cardiac imaging modalities are able to visualize the left atrium (LA) and, therefore, allow for quantification of both structural and functional properties of this cardiac chamber. In echocardiography, only the maximal LA volume is included in the assessment of diastolic function at the current moment. Numerous studies, however, have shown that functional measures may be superior to the maximal LA volume in several aspects and to possess clinical value even in the absence of structural abnormalities. Such functional measures could prove particularly useful in the setting of predicting atrial fibrillation, which will be a point of focus in this review. Pivotal cardiac magnetic resonance imaging studies have revealed high correlation between LA fibrosis and risk of atrial fibrillation recurrence after catheter ablation, and subsequent multimodality imaging studies have uncovered an inverse relationship between LA reservoir function and degree of LA fibrosis. This has sparked an increased interest into the application of advanced imaging modalities, including both speckle tracking echocardiography and tissue tracking by cardiac magnetic resonance imaging. Even though increasing evidence has supported the use of functional measures and proven its superiority to the maximal LA volume, they have still not been adopted in clinical guidelines. The reason for this discrepancy may rely on the fact that there is little to no agreement on how to technically perform deformation analysis of the LA. Such technical considerations, limitations, and alternate imaging prospects will be addressed in this review. (Circ Cardiovasc Imaging. 2016;9:e004947. DOI: 10.1161/CIRCIMAGING.116.004947.)

Key Words: atrial fibrillation • cardiac computed tomography • cardiac magnetic resonance imaging • echocardiography • left atrium • positron emission tomography

Atrial Function in Health and Disease

Left Atrial Phases and Physiological Changes

Throughout the cardiac cycle, the left atrium (LA) works in 3 distinctive ways: (1) during ventricular systole, it functions as a reservoir for the storage of blood entering from the pulmonary veins, (2) at early ventricular diastole, it works as a conduit for the passive passage of blood to the left ventricle (LV), and (3) it contributes to LV filling with an active atrial contraction. Both the reservoir and conduit function of the LA are determined by LA myocardial compliance and the longitudinal displacement of the LV, whereas LA contraction, to a greater extent, is influenced by LV filling pressures. All of these functions are modulated by physiological conditions, that is, during exercise, which elevates the heart rate and, thereby, influences preload and afterload conditions. Likewise, senescence also influences the contribution of the different LA phases to LV filling: with increasing age, a decrease in reservoir and conduit function is observed, but fortunately this is remedied by a compensatory increase in LA contraction. Thus, changes in the function of the different phases are natural occurrences, which are either transient (as during exercise) or more permanent (as with increasing age). For most part, however, these changes in phasic LA functions are without consequence because the phases are interdependent and are meant to compensate for each other. This ability to adapt between the different phases is an important prerequisite for ensuring LV filling. Should this adaptiveness be lost (ie, loss of atrial contraction during atrial fibrillation [AF]), a corresponding loss in cardiac output is one of the consequences that can be expected.

Pathophysiological Failure of Atrial Function

As mentioned earlier, transient changes in loading conditions influence LA function, but naturally so does more pathological and permanent changes in loading conditions, as seen...
with, for example, hypertension or aortic stenosis. In these settings of elevated LV afterload, an initial decline in LA conduit function is observed, which is compensated for by an increased LA contraction to drive an efficient LV stroke volume. Besides ensuring adequate LV filling, the amplified LA contraction also propagates a reflux to the pulmonary venous circuit, resulting in increased LA preload, which eventually causes LA dilation. Progressive LA dilatation results in myocardial disarray, which compromises LA contraction. Accordingly, diminishment and complete loss of atrial contraction as a compensatory mechanism has proven to predict cardiovascular outcome in patients with cardiomyopathy, because it represents a late stage in the atrial disease process.

A similar situation is recognized in the development of AF. The development of AF, however, may not necessarily be facilitated by LA dilation, but rather relate to fibrotic lesions within the myocardium. These fibrotic lesions allow for reentry circuits to emerge, and these reentry circuits can induce and perpetuate AF in the atrium. The hallmark of AF is the loss of atrial contraction, which reduces LV filling and cardiac output and instead creates a volume overload for the LA. This volume overload causes progressive LA dilation with increasing myocyte disarray and increasing fibrotic changes, which upholds the AF condition, creating a vicious cycle, and finally results in atrial fibrillation.

**Limitations of Left Atrial Volumes**

Limitations of LA volumes have been recognized by the recently convened task force report for multimodality imaging in AF. In recent years, there has been an increased focus on the detection of new-onset AF, and studies are being conducted to evaluate whether implantable loop recorders should be applied clinically to enhance AF detection and, thereby, prevent strokes in select patient groups. The potential implementation of such expensive and invasive monitoring devices stresses the need for a better selection of patients in need of prolonged monitoring and close follow-up. The assessment of LA function could play a vital role in this selection process. However, not only new-onset AF has been of interest, but also AF recurrence in those who undergo rhythm conversion (either by cardioversion or catheter ablation), as will be discussed in depth later on.

**Echocardiography**

Quantitative assessment of LA function can be readily performed by several echocardiographic modalities, with the most widely investigated being 2-dimensional (2D) volume measures and LA speckle tracking.

**Left Atrial Volumes**

**Principles of Left Atrial Volumes**

For now, the only measure of the LA to be included in the clinical guidelines is the maximal volume measured at LV end systole (LAV$_{\text{max}}$). This measure has proven to be an independent predictor of cardiovascular outcomes, including incident AF. Enlargement of the LAV$_{\text{max}}$, however, often occurs as a result of chronic pressure overload and is likely preceded by changes in LA functional measures. Accordingly, LA functional parameters have, on several occasions, proven useful for predicting outcome in patients without enlarged LA. Hence, other LA measures could be valuable: these include the minimal volume obtained at the LV end-diastole (LAV$_{\text{min}}$) and the volume obtained at p wave onset (pre atrial contractile volume; LAV$_{\text{p}}$). In combination with LAV$_{\text{max}}$, these can provide insight on the amount of blood flow in the LA throughout the atrial phases (Figure 1), which allows for calculation of fractional volume changes as markers of LA function (Table 1). The most recent guidelines recommend measuring the LA volume by the biplane disk method from the apical 4- and 2-chamber view at end systole (Figure 2A). Care should be taken to avoid foreshortening in the apical window because this will give a false impression of LA dimensions. Furthermore, both pulmonary veins and the LA appendage should be excluded from the volume measurement. LA volume assessment already represents an integral part in the evaluation of diastolic function, and a LAV$_{\text{max}}$ >34 mL/m$^2$ is used to differentiate between different diastolic dysfunction grades. However, there is more information to gain from LAV$_{\text{max}}$ other than simply grouping patients into LAV$_{\text{max}}$ >34 mL/m$^2$ or not. For patients with mitral regurgitation (Figure 2B), progressive LA dilation by the LAV$_{\text{max}}$ is a valuable measure of chronicity and, hence, also a strong predictor of cardiovascular outcome.
by 2D imaging may not reflect true atrial structure, and this cannot be rectified by myocardial tracking, but perhaps by 3D imaging instead.

Three-Dimensional Volume Acquisition

The geometric assumptions made by 2D imaging is an unfortunate limitation that may be remedied by 3D imaging (Figure 1), which has proven superior for volume acquisition of the LV. Echocardiographic guidelines now state that 3D volume acquisition for the LV is preferred over 2D and should be the method of choice whenever possible. The same could be expected for the LA once dedicated software and normative values have been validated and more widely established. 2D volume acquisition relies on complex geometric assumptions, both in the Simpson’s biplane and area–length methods, but 3D tracking of the LA are not dependent on such technical assumptions, and concordance studies with comparison against cardiac magnetic resonance imaging (CMR) have found it to be more accurate than 2D imaging. Additionally, it has been established that 3D LA volume is superior for longitudinal follow-up and sequential measurements in patients. 3D imaging acquisition, however, requires cooperation from the patient, reliable measures require high imaging quality, and also requires frame-stitching over consecutive cardiac cycles, which cannot be done in the presence of irregular R-R-interval, that is, during AF rhythm. Furthermore, lacks of widely established normative values along with the influence of vendor-dependency in the methodology for tracking the LA are still major limitations. This is aggravated by the fact that many studies have investigated LA volume acquisition by the use of software dedicated to the LV and not specifically designed for LA measurement. Even though the European Task Force shares the viewpoint that 3D volume acquisition should be the method of choice in the future, there are still lots of limitations to reconcile before implementation becomes relevant. Current focus should be on facilitating the replacement of LAV\textsubscript{max} instead of using the LA dimension from the parasternal long-axis view (Table 2).

Left Atrial Strain

Principles of Atrial Strain

Atrial strain is a direct measure of myocardial tissue properties and can be evaluated by different modalities. Speckle

<table>
<thead>
<tr>
<th>Left Atrial Measures</th>
<th>Index Calculation</th>
<th>Reservoir</th>
<th>Conduit</th>
<th>Contraction</th>
<th>Normal Values\textsuperscript{10}</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAEF, %</td>
<td>Total emptying volume/LAV\textsubscript{max}</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>70±9</td>
</tr>
<tr>
<td>LApEF, %</td>
<td>Passive emptying volume/LAV\textsubscript{max}</td>
<td>x</td>
<td></td>
<td></td>
<td>44±12</td>
</tr>
<tr>
<td>LAaEF, %</td>
<td>Active emptying volume/LAV\textsubscript{pre}</td>
<td></td>
<td>x</td>
<td></td>
<td>47±12</td>
</tr>
<tr>
<td>LAI, %</td>
<td>Total emptying volume/LAV\textsubscript{res}</td>
<td>x</td>
<td></td>
<td></td>
<td>272±126</td>
</tr>
</tbody>
</table>

LAEF indicates left atrial active emptying fraction; LAEF, left atrium emptying fraction; LAI, left atrial expansion index; LApEF, left atrial passive emptying fraction; LAV\textsubscript{pre}, left atrial end-systolic volume; LAV\textsubscript{res}, left atrial end-diastolic volume; and LAV\textsubscript{max}, left atrial volume at onset of the p wave.
Speckle tracking echocardiography acquires 3 overall strain values and 3 strain rate values (Table 3). On mitral valve opening, the peak atrial longitudinal strain (PALS) is observed and is a reflection of LA reservoir function. Just before LA contraction (defined as p wave onset), a plateau phase is seen in the strain curve, and this plateau strain value (ALSlate) is a measure of the deformation elicited by atrial contraction. Finally, the conduit function can be calculated as the difference between PALS and ALSlate (Figure 3 and Table 3). Besides the absolute strain values, strain rate values also provide insight into atrial phasic function (Figure 4). For the LV, myocardial speckle tracking seems to provide a more comprehensive insight in cardiac mechanics than simple volume measures and has consequently shown to provide clinical information, which often goes undetected by volume measures. As a result, speckle tracking is now being gradually implemented in clinical guidelines. Myocardial speckle tracking of the LA could be just as useful for assessing LA mechanics. This technique, however, is faced with some technical challenges, which need to be addressed (Table 4).

**Limitations of Atrial Strain**

Speckle tracking has some intrinsic limitations, which apply for both LA and LV analysis. Besides such inherent limitations, LA speckle tracking suffers from a lack of consensus on how to perform proper tracking. For instance, some studies only trace the atrium in the 4-chamber view, others use biplane, and some use triplane. Several practical
Table 2. Key Points From the European Task Force for Multimodality Imaging in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>Cardiac magnetic resonance imaging (CMR)</th>
<th>Cardiac computed tomography (CT)</th>
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<tbody>
<tr>
<td>• Patients with atrial fibrillation should have an echocardiogram performed to assess cardiac structure and function.</td>
<td>• Up to now, there is neither recommendation nor expert consensus on the role of late gadolinium enhancement CMR to assist atrial fibrillation ablation procedures. The available data are intriguing enough to warrant further research.</td>
<td>• Further studies investigating the association between atrial arrhythmia and epicardial adiposity are needed. No real clinical impact has been demonstrated yet.</td>
</tr>
<tr>
<td>• Maximal left atrial volume indexed to body surface area is recommended for quantification of left atrial size and should be preferred over left atrial dimension obtained from the parasternal long-axis view.</td>
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<tr>
<td>• The left atrial lateral wall strain can be reliably imaged and is not constrained by other cardiac chambers and may be used as the best surrogate of left atrial wall fibrosis by cardiac magnetic resonance imaging.</td>
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<tr>
<td>• A left atrial strain (in systole) &lt;30% indicates significant alteration of left atrial reservoir function, which predicts poor outcome.</td>
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<tr>
<td>• Left atrial strain should be measured from the R-wave of the ECG in atrial fibrillation. The beginning of the p wave should be preferred in sinus rhythm.</td>
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<tr>
<td>• Assessment of left atrial volumes by 3D echocardiography will have to be implemented in clinical practice. It is still not available widely, but it has been demonstrated as really valuable. Like left ventricular volume by 3D echocardiography, it has been proposed as superior to the 2D approach that remains the standard approach.</td>
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Table 3. Left Atrial Strain Measures and Phasic Function

<table>
<thead>
<tr>
<th>Left Atrial Measures</th>
<th>Reservoir</th>
<th>Conduit</th>
<th>Contraction</th>
<th>Normal Values*</th>
<th>Normal Values†</th>
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<tbody>
<tr>
<td>Peak atrial longitudinal strain, %</td>
<td>×</td>
<td></td>
<td></td>
<td>46.8±7.7</td>
<td>35.6±7.9</td>
</tr>
<tr>
<td>Early diastolic longitudinal strain, %</td>
<td>×</td>
<td></td>
<td></td>
<td>27.3±6.4</td>
<td>21.4±6.7</td>
</tr>
<tr>
<td>Late diastolic longitudinal strain, %</td>
<td>×</td>
<td></td>
<td></td>
<td>19.6±4.2</td>
<td>14.2±3.3</td>
</tr>
<tr>
<td>Systolic strain rate, s⁻¹</td>
<td>×</td>
<td></td>
<td></td>
<td>2.4±0.5</td>
<td>2.0±0.6</td>
</tr>
<tr>
<td>Early diastolic strain rate, s⁻¹</td>
<td>×</td>
<td></td>
<td></td>
<td>−2.5±0.7</td>
<td>−2.0±0.6</td>
</tr>
<tr>
<td>Late diastolic atrial strain rate, s⁻¹</td>
<td>×</td>
<td></td>
<td></td>
<td>−2.8±0.6</td>
<td>−2.3±0.5</td>
</tr>
</tbody>
</table>

*Normal values±standard deviation with QRS as onset.†Normal values±standard deviation with p wave as onset.

p-wave and QRS-complex. A proper consensus is required because these presets potentially influence the absolute strain values. This was highlighted in an editorial by Jellis and Klein, illustrating that the atrial phasic strain values diverge simply depending on whether the reference point is set at QRS onset or p wave onset. Nevertheless, it is the recommendation by the European task force that the ECG reference point should be determined with respect to whether the patient is in AF or sinus rhythm. The European Task Force also recognizes that the normative values, which have been presented for LA strain, differ substantially depending on whether the reference point is set at the p wave or QRS onset. The reason for this apparent difference is unclear, and no research study has been undertaken to examine whether the reference point really influences the absolute values. However, given that it should simply reflect a baseline drift, the large differences in normative values may reflect vendor-dependency, lack of appropriate methodology, and lack of dedicated software for LA analysis. No matter the cause, we can ascertain that there seems to be a difference in normative values as presented by Sun et al. and Saraiva et al., and 2 sets of normative values simply depending on ECG reference point makes the interpretation for a clinician complicated. This speaks against using p wave onset in one setting and QRS onset in another setting as suggested by the European Task Force. This approach is not likely to promote more uniformity in future studies and could impede the implementation of LA strain. To aid in standardization of the technique, we think the implementation (if necessary) would be facilitated by recommending one method. Because AF patients do not have a p wave, it seems most appropriate to use the QRS as onset. Particularly, for patients undergoing ablation or other rhythm conversion, recommending different methodology based on rhythm state may be an unfortunate approach for longitudinal follow-up, given the discrepancy in strain values.
Figure 3. Left atrial (LA) speckle tracking echocardiography and deformation curves. A. Deformation curves when the LA speckle tracking is triggered of the QRS-onset. B. The deformation curves when the LA speckle tracking is triggered of the p wave. For both cases, the whole LA in the apical 4-chamber view is traced, and the white dotted line denotes the global longitudinal LA strain values. For both figures, the reservoir function is presented by the white arrow, atrial contraction is presented by the orange arrow, and the conduit function by the blue arrow.
Figure 4. Strain rate curves from left atrial speckle tracking echocardiography. A, Strain rate curves when the left atrial speckle tracking is triggered of the QRS-onset; B, The strain rate curves when the left atrial speckle tracking is triggered of the p wave. Systolic strain rate denotes the rate at which the left atrial expansion occurs and reflects reservoir function. Early diastolic strain rate is a reflection of the rate at which the left atrium is compressed by left ventricular relaxation and, thus, reflects the conduit function. Late diastolic strain rate represents the rate at which the left atrium actively contracts.
Table 4. Current Limitations in Atrial Speckle Tracking

<table>
<thead>
<tr>
<th>Overall Limitations</th>
<th>Apical 4 Chamber</th>
<th>Apical 2 Chamber</th>
<th>Apical 3 Chamber</th>
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<tr>
<td>Loading dependency</td>
<td>Inclusion of atrial roof</td>
<td>Inclusion of atrial roof</td>
<td>Inclusion of atrial roof</td>
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<tr>
<td>Angle dependency</td>
<td>Pulmonary venous structure</td>
<td>Pulmonary venous structure</td>
<td>Pulmonary venous structure</td>
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<tr>
<td>Frame rate</td>
<td>Inclusion of atrial septum</td>
<td>Pulmonary venous structure</td>
<td>Pulmonary venous structure</td>
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<tr>
<td>Spatial resolution</td>
<td>Fibromuscular tissue</td>
<td></td>
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<tr>
<td>Selection of uni-, bi-, or triplane</td>
<td>Impact of septal defects</td>
<td>Inclusion of anterior wall</td>
<td>Inclusion of anteroseptal wall</td>
</tr>
<tr>
<td>Selection of ECG reference point</td>
<td>Impact of atrial septal aneurysm</td>
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<tr>
<td>Differential width adjustments</td>
<td>Impact of right atrial pressure</td>
<td>Impact of left atrial appendage</td>
<td>Partly inclusion of ascending aorta</td>
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<td>Vendor-dependent values</td>
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Three-Dimensional Atrial Strain

Although the limitations may immediately seem overwhelming, extensive research has been performed, and normal reference values for the different atrial strain measures have even been proposed. Additionally, some consistent and promising results have been provided for atrial speckle tracking, particularly for the prediction of AF recurrence after ablation (see later). Furthermore, many obstacles may be overcome by the advent of automated software and 3D imaging in which atrial speckle tracking has shown promise. Automated 3D speckle tracking would allow for highly reproducible tracking and assessment of reliable LA volumes without geometric assumptions (as mentioned earlier) and would also be able to track speckles along all longitudinal dimensions. Often, the validity of speckle tracking in 2D is weakened by the fact that speckles can move out of the 2D imaging plane along the z axis and are, therefore, not tracked throughout the entire cardiac cycle. Finally, 3D imaging could provide a comparative assessment with electromechanical and electroanatomical mapping, which could contribute pathophysiological insight in AF.

Potential and Future Directions of Atrial Strain

Overall, atrial speckle tracking seems a promising tool of potential clinical value, but which still requires technical refinement and associated practical guidelines as have been devised for ventricular speckle tracking. Hopefully, the recent consensus statement by the European task force recommending LA speckle tracking to be performed only in the lateral wall will uniform future research studies and ease the interpretation of these findings. Important to note, however, is that this recommendation is somewhat unfounded because technical studies on regional disparities and the overall impact of regional LA strain remain largely unexplored. A prerequisite for the implementation of LA speckle tracking is the development of automatic speckle tracking software dedicated to the LA. Even though some software has been developed, it is imperative, as illustrated in the study by Addetia et al., that such software accommodates the highly varying myocardial width of the LA to ensure reliable strain values.

Potential Clinical Application: Ablation Procedure

The clinical potential of assessing LA mechanical dysfunction is far reaching and beyond the scope of this review. The ability to predict paroxysmal AF in high-risk subjects (ie, cryptogenic stroke patients) and the recurrence of AF after cardioversion and catheter ablation could improve the clinical management of AF patients, and LA imaging could help guide this process. Particularly, the recurrence of AF after catheter ablation has been subject to much research. Identification of patients who may be nonresponsive to ablation therapy would reduce unnecessary procedures and, hence, reduce both procedure-related costs and complications. Because all patients who undergo an ablation procedure will have an echocardiogram performed, a detailed analysis of LA mechanics could help identify patients who may be refractory to treatment. As discussed later on, CMR late gadolinium enhancement (LGE) studies and histological studies have shown that recurrence of arrhythmias after ablation is directly related to the amount of fibrosis before ablation. Because reservoir function by LA speckle tracking has shown a linearly inverse relationship to CMR LGE–detected fibrosis, preprocedural reservoir function may well be a strong predictor of successful outcome. A clinical approach on how to manage AF patients based on the Utah classification has been proposed and states that patients in stage III–IV should be carefully reconsidered for undergoing ablation. Given the close inverse relation with atrial strain, this implies that an optimal cutoff value of PALS could be presented and help guide management in patients undergoing first-time ablation. Another intriguing approach is to look at the improvement in reservoir function after ablation. This could be of value for the early recognition of patients who experience a recurrence of AF and in whom a second ablation is considered. As mentioned previously, however, the technical considerations in atrial strain limits its application, and further multimodality imaging studies are needed to translate the CMR LGE staging system (Utah classification) into a comparative atrial strain staging system, with atrial strain values corresponding to each stage of the Utah classification.

Competing Echocardiographic Measures

Besides the previously mentioned LA volumes, there are several other potential echocardiographic markers that could be used for the detection of AF. Recent research findings have raised the question as to whether PALS has clinical value beyond what we can obtain by the ventricular global longitudinal strain (GLS). This measure has proven to be an independent predictor of AF in the general population, with authors stating that this may reflect an impaired reservoir function. Furthermore, studies have shown that the prognostic value of PALS may be largely driven by GLS and LAVmax. This
may be because both measures reflect LA reservoir function. Therefore, simply recognizing GLS as also being a measure of LA reservoir function could be sufficient and, thereby, preclude the implementation of PALS. This approach has several advantages (Table 5) and is clinically appealing because GLS is already being implemented into guidelines. Unfortunately, the majority of studies investigating the value of atrial strain seldom report GLS and whether or not this measure influences the prognostic value of PALS. To clarify the role of these 2 variables, it would be beneficial for future studies investigating the application of atrial strain to include GLS. A recent study by Addetia et al examined simultaneous speckle tracking of the LV and LA in healthy subjects and found a difference in the time-to-peak value, which seems to occur later in the cardiac cycle for PALS than for GLS. This could prove important because measures of LA dyssynchrony have also been proposed to predict AF. The rationale for investigating LA dyssynchrony is that there is a heterogeneous pattern in LA fibrosis and dysfunction, which can be detected by this more regional analysis rather than by looking at global LA strain values. Interatrial dyssynchrony, defined both as maximal time to peak delay to the opposing atrial wall and as mechanical dispersion (standard deviation of time-to-peak), has shown promise for the prediction of recurrence after ablation and has been shown to be superior to PALS. In conclusion, atrial reservoir strain has shown a close relationship to CMR-detected LA fibrosis and may be a key marker for the prediction of AF recurrence. Other markers of LA reservoir function, such as GLS, could, however, have similar potential and would be more easily applied.

Cardiac Magnetic Resonance Imaging

Volumetric Measurements
CMR is gold standard for cardiac volumes, but traditionally CMR has not been used for patients with AF because of the limitation that CMR depends on a regular heart rhythm to produce meaningful images. Feasibility and high reproducibility for measuring atrial volumes with CMR has, however, been confirmed, even with an irregular heart rhythm. It has been demonstrated with CMR that patients with persistent AF have larger LA volumes compared with those with paroxysmal AF. Additionally, LA volumes were found to be similar in patients with persistent versus permanent AF but significantly larger than in healthy volunteers, suggesting that dilation of the atrias do not progress between 2 stages. Ablation and cardioversion studies have shown that even ≤6 to 12 months after restoration to sinus rhythm, LA function is still not restored, but rather seems to improve continuously. This suggests that some degree of reverse remodeling may be possible when sinus rhythm is achieved. Even though functional assessment is still not widely used in clinical practice for AF patients, in recent years, new methods for evaluating atrial function and fibrosis using CMR have emerged.

Atrial Fibrosis
LGE is a well-validated method for detecting fibrosis in the myocardium. The method uses the qualities of gadolinium contrast agents. Gadolinium is water-soluble and distributes throughout the extracellular space, which results in greater accumulation of gadolinium where fibrosis is present, causing enhancement in areas of fibrosis (Figure 5). Initially, the LGE technique was modified by Peters et al for the use of visualizing fibrosis in the LA (LGE), and in recent years, LGE determination has greatly improved. This is especially because of the extensive work by the Utah group, which has refined the technique and developed a staging system where the degree of fibrosis is divided into stages I–IV. This staging system has in a recent large multicenter study, the DECAAF study (Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation), including >200 patients, defined 4 stages of severity of atrial fibrosis: stage 1 (<10%) of the atrial wall; stage 2 (10%; <20%); stage 3 (20%; <30%), and stage 4 (≥30%). The DECAAF study and other studies have now made it widely accepted that patients with more extensive LA LGE before ablation have a higher risk of AF recurrence after ablation compared with patients with less LA LGE but there is still some debate on how to translate this knowledge into clinical practice. Minimal scar formation (minimal LA LGE) after ablation has been associated with a higher recurrence of AF which has shown potential for assisting in ablation procedures and the possibility of increasing the success rate for future ablations. Already, the Utah group recommends that patients with diffuse stage III and stage IV fibrosis are not to be subjected to ablation but treated medically instead.

The method has been validated in several studies that have found a strong association between regions with LA LGE and low voltage on electroanatomic mapping, which has also been supported by histological samples. Furthermore, the Utah group has confirmed that increased degrees of LA LGE are related to decreased function assessed by echocardiographic speckle tracking, as discussed earlier.

Despite the promising aspects of the technique, it is still not widely used in daily clinical practice. The LGE technique has long been used for the thick ventricular wall, but acquiring useful images of the thin wall of the atria requires specialized training. This includes setting up well-working ECG gating, respiration gating, and properly adjusting inversion times for nulling the myocardium at the right time after gadolinium injection. Postprocessing analyses are highly time-consuming, and specialized training is also needed to ensure accurate segmentation of the LA, defining thresholds

<table>
<thead>
<tr>
<th>Advantages of Applying Global Longitudinal Strain</th>
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<tr>
<td>Already being implemented clinically</td>
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<tr>
<td>Automatic software available and in use</td>
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<td>Established guidelines on proper tracking</td>
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<td>Better image resolution</td>
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<td>Established predictor of atrial fibrillation</td>
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<tr>
<td>Has seldom been examined in studies investigating the value of peak atrial longitudinal strain</td>
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<tr>
<td>Has proven to drive prognostic value of peak atrial longitudinal strain in some studies</td>
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for enhanced regions and making sure potential artifacts are excluded.69,70,73,76 Hence, there are many challenges in applying LA LGE determination in clinical practice.69 Additionally, experts in the field still need to agree on a common methodology to secure comparable results between international research centers.61 Standardized protocols and intensity scores have been proposed to meet these challenges but, unfortunately, these have not yet been successful.59,62

Although most LA LGE research has focused on symptomatic AF and outcomes after ablation, the method has also supported the development of the fibrotic atrial cardiomyopathy theory by Kottkamp.63 This theory has questioned the present understanding that AF begets AF,64 arguing that even though patients with persistent AF may, on average, have higher degrees of LA LGE compared with paroxysmal AF patients,34,52 the variability of the extent of fibrosis is substantial. Hence, some patients with paroxysmal AF present with extensive LA LGE and some patients with persistent AF present with little LA LGE and may never progress further.65 These intriguing aspects warrant further investigation into the natural history of AF, and on this matter, LA LGE may turn out to be valuable.

Atrial Tissue Tracking
In recent years, a new way of evaluating the deformation of the atrial wall during the cardiac cycle has emerged. Tissue tracking, corresponding to speckle tracking measured with echocardiography, has been used for quantifying cardiac deformation in the ventricles and has recently been adapted for use to quantify atrial deformation (Figure 6). To date, results have been promising, and the method has performed well in feasibility, validation, and reproducibility studies.65,66 Results from MESA (Multi-Ethnic Study of Atherosclerosis) have indicated that myocardial scar is associated with lower LA strain and strain rate.67

Despite these encouraging conclusions, this technique is also faced with the challenges of the thin atrial wall, the difficult and varying anatomy of the LA with the presence of pulmonary veins and LA appendage, and the complex physiology of the LA. But where acquiring LA LGE images is a specialized skill, tissue tracking makes use of standard CMR images (steady-state free precession).65 Another problem with tissue tracking measured with CMR is the low temporal resolution of 20 to 40 ms. In conclusion, novel CMR techniques show promising results, and despite the current challenges of LA LGE and tissue tracking, these new methods may change the way we understand AF and improve treatment of AF via personalized treatment.

Applications of Cardiac Computed Tomography in Atrial Fibrillation
Cardiac computed tomography (CT), in addition to the assessment of coronary arteries, is useful in a range of noncoronary applications. Although radiation exposure is a limitation of cardiac CT, technological advances now allow for cardiac imaging, with effective radiation doses as low as 1 mSv with high image quality. The high spatial resolution and excellent 3-dimensional definition provided by cardiac CT has made it the method of choice in a variety of settings in patients with AF.

Left Atrial Structure
Cardiac CT allows for the assessment of detailed anatomic information of the LA (Figure 7) and LA appendage, and several parameters have been found to be predictors of AF and thromboembolic stroke in patients with AF.68–70 Furthermore, cardiac CT reference material of normal values of cardiac chamber sizes has recently been published, allowing for accurate determination of abnormal volumetric measurements when using cardiac CT.71 More research with regards to the clinical applicability of cardiac CT for risk stratification in patients with AF is, however, required.

Epicardial Adipose Tissue
The pathophysiological mechanisms of AF are not yet fully understood. Current data suggest activation of inflammatory pathways, possibly triggered by proinflammatory cytokines in epicardial adipose tissue (EAT), may be important prerequisites of AF.72,73 Cardiac CT has been found to be an excellent modality for the quantification of EAT. Results from the Framingham study have shown that EAT by cardiac CT closely relates to cardiovascular outcome and have furthermore presented normal values of 124±50 mL obtained from 1267 individuals.74 Several studies have suggested that
EAT may serve as a source of proinflammatory cytokines, contributing to fibrotic remodeling of the atrial myocardium, and ultimately to the pathophysiology of AF. Associations between density, volume, and thickness of EAT and the risk, persistence, and severity of AF have been found. More research is needed, however, to determine the predictive capabilities of EAT and AF burden. Currently, quantification of EAT by cardiac CT is not included in guidelines for risk stratification (Table 2).

**Left Atrial Wall Thickness**

Changes in LA myocardial wall thickness (LAWT) have been identified as an important part of the remodeling process seen in patients with AF and is based on the critical mass hypothesis, which states that to sustain AF, a certain critical mass of tissue must be present. Cardiac CT has high spatial resolution, and true volume coverage of the heart makes it a realistic and attractive modality for the quantification of structural abnormalities. This information may be used to guide radiofrequency catheter ablation delivery in regions based on their tissue thickness. Nakamura et al found that cardiac CT–determined anterior LAWT was significantly thicker in patients with paroxysmal AF (LAWT 2.4±0.2 mm) when compared with a group with no history of AF (LAWT 1.9±0.2 mm) and a group with non-paroxysmal AF (LAWT 2.1±0.2 mm), suggesting that not only patients with AF can be identified based on anterior LAWT, but also the transition from paroxysmal AF to persistent AF can be predicted using LAWT. Further development of automated measurement techniques and standardized algorithms for the correct and reproducible discernment of the epicardial and endocardial borders of the LA using cardiac CT is required. In conclusion, cardiac CT currently plays an integral role in the assessment of the AF patient. Future developments of novel CT techniques are expected to expand the usage of cardiac CT within treatment, monitoring of disease, and risk stratification of AF.

**Future Directions**

Throughout the review, we have presented some important limitations and some intriguing aspects for each modality.
that we think would benefit from additional research to clarify the role of these imaging modalities in AF. Besides considering the specific techniques, such as echocardiographic strain and CMR tissue tracking, it is also important to consider the availability, inherent benefits, and limitations that adhere to the imaging modality itself, which are presented in Table 6, because these considerations greatly influence the clinical feasibility of a specific imaging modality. The review has focused primarily on the modalities that have been subject to much research, but we would like to encourage research for a modality that may have been overlooked: nuclear imaging. This could be valuable considering its ability to identify inflammatory processes, which, as mentioned earlier (see CT section), could play a vital role in the process of developing AF.

### Table 6. Crude Comparison Between Cardiac Imaging Modalities

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Radiation</th>
<th>Time-Consuming</th>
<th>Already Applied in AF (Preablation)</th>
<th>Detailed Anatomy</th>
<th>Availability</th>
<th>Promising Research Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>−</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>Left atrial strain</td>
</tr>
<tr>
<td>Cardiac magnetic resonance imaging (CMR)</td>
<td>−</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>Late gadolinium enhancement and tissue tracking</td>
</tr>
<tr>
<td>Cardiac computed tomography (CT)</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Epicardial adiposity</td>
</tr>
<tr>
<td>Positron emission tomography (PET)</td>
<td>+</td>
<td>++</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>None, but warrants studies</td>
</tr>
</tbody>
</table>

− indicates none; +, minor; ++, moderate; ++++, major; and AF, atrial fibrillation.

### Role of Positron Emission Tomography in Atrial Fibrillation

AF is predominantly secondary to structural heart disease, and cardiac positron emission tomography (PET) is, in many cases, helpful in the investigation of the underlying cause. Myocardial PET imaging can demonstrate the presence of coronary artery disease and—in chronic ischemic heart failure—myocardial viability. Inflammatory processes such as sarcoidosis and myocarditis can also be visualized. Because of the high activity in the LV, the thin-walled chambers of the heart—the right ventricle and the atria—are normally not seen with the PET modality. These structures may, however, be visualized if tracer uptake in the LV is low or absent. The radioligand 18fluoro-deoxyglucose (18FDG) is a widely used marker of tissue glucose metabolism, and

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Figure 7. Volume acquisition and structural view by cardiac computed tomography. **A**, Determination of left atrial volume (red line), excluding pulmonary veins. **B**, Determination of left atrial volume (red line), excluding left atrial appendage. **C**, Determination of left atrial volume (red line) with border to the left ventricle at the level of the mitral annulus. **D**, Three-dimensional view of the left atrium with pulmonary veins and left atrial appendage. LA indicates left atrium; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; LV, left ventricle; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.
18FDG PET may be used to detect cardiac inflammation (Figure 8). Normal myocardial tissue can be switched to free fatty acid metabolism by means of a low carbohydrate diet and intravenous administration of low-dose heparin.91 This allows for a high contrast between normal myocardium and areas with increased glucose uptake, that is, areas with ongoing inflammatory processes. Though poor image resolution remains an important limiting factor, cardiac PET may potentially visualize pathology of the thin atrial and right ventricle walls. Especially, the hybrid PET/magnetic resonance imaging scanner may allow for the fusion of functional and high-resolution anatomic images but the modality is still in its infancy.92 Incidental atrial 18FDG uptake is reported in 0.4% of oncological patients examined with 18FDG PET and is associated to AF.93,94 Causes such as atrial overload and lipomatous hypertrophy of the interatrial septum—a condition that has also been associated with atrial arrhythmias—have been established.95,96 Inflammatory processes such as sarcoidosis and myocarditis may involve the atrial walls,97,98 and because AF is not uncommon in these cases,18,99FDG PET could play a vital role, although this field remains largely unexplored. For now, the role of PET imaging remains unclear but one of potential value, particularly in patients with well-established inflammatory disease states, in whom a search for occult AF seems justified.

Conclusion
The assessment of atrial function is becoming increasingly relevant because several trials are being conducted to investigate whether prolonged cardiac rhythm monitoring by implantable devices should be applied for the detection of AF in the future. A race for finding appropriate surrogate markers for AF has begun, and several imaging modalities are being heavily investigated for this purpose. We have to recognize, however, the limitations pertaining to advanced modalities that warrant clarification, and there is a need for additional technical studies before these otherwise promising imaging techniques can be applied clinically. Owing to multimodality imaging studies, there is strong evidence suggesting that atrial fibrosis and LA reservoir function directly relates to risk of AF recurrence after ablation. How we should translate this knowledge into clinical practice remains to be seen.

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References


Int adiposity with the presence and severity of non-valvular atrial fibrillation.


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