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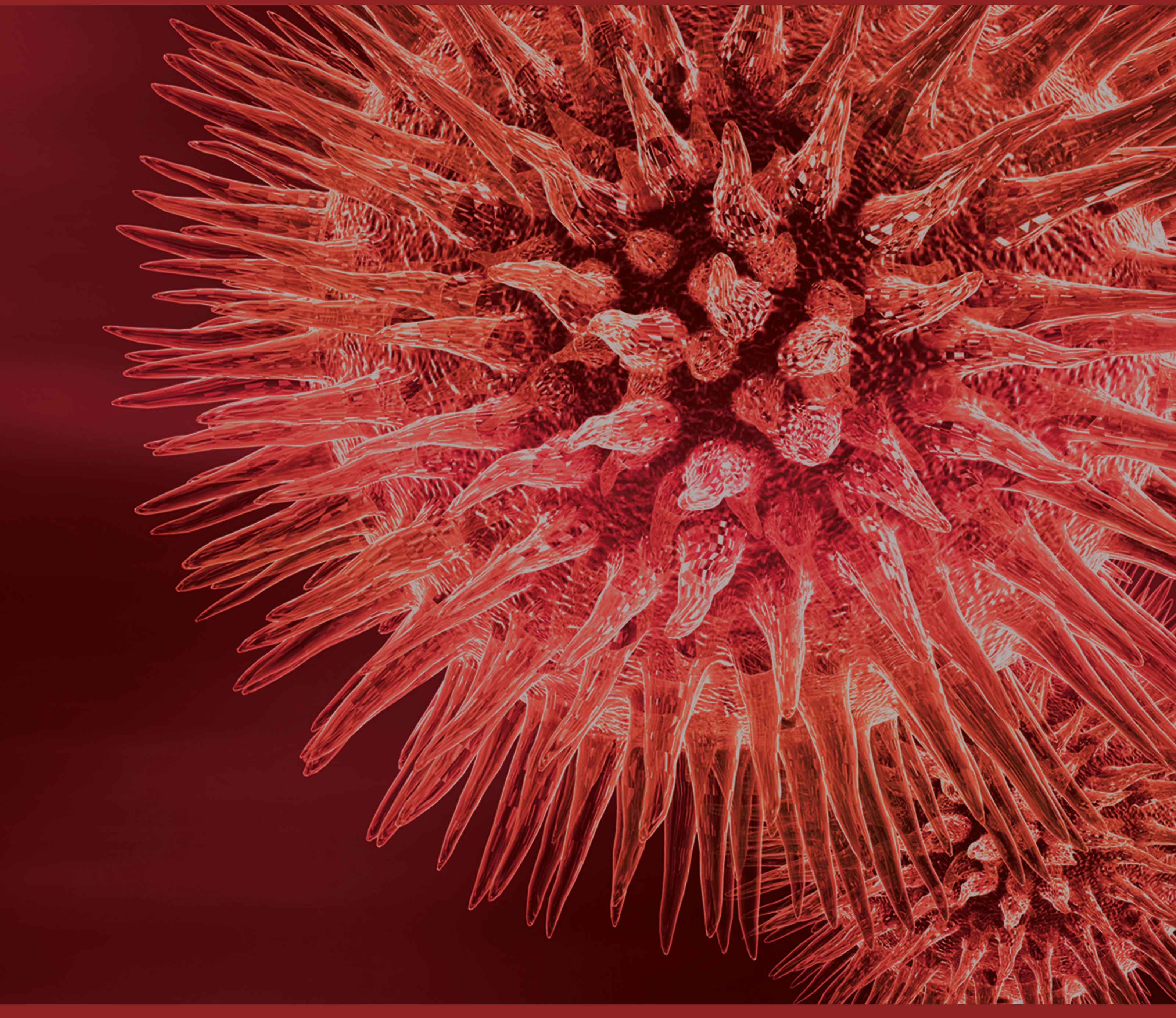
New Insight in the Assessment of Atrial Size and Function

Guest Editors: Giovanni Di Salvo, Nassir Marrouche, Masaaki Takeuchi, and Marcel Borgers



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Editorial

New Insight in the Assessment of Atrial Size and Function

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The atrium has been considered for too many years a neglected chamber and because of this the assessment of atrial function is still a challenge.

More recently, new noninvasive diagnostic modalities have shed new light on atrial role in several diseases.

The assessment of atrial function may have particular relevance for the growing epidemic of atrial fibrillation which currently affects nearly 2% of the general population, with prevalence expected to double by 2050.

A better knowledge and understanding of atrial function in different cardiac diseases (mitral valve disease, cardiomyopathies, coronary artery disease, heart failure, hypertension, congenital heart diseases, etc.) may have a significant clinical impact in the management and in the prognostic evaluation of our patients.

This special issue focuses on original research articles and review papers that address a broad range of mechanisms associated with atrial dysfunction, with possible prognostic and therapeutic interventions.

In this dedicated issue, R. Leischik et al. reviewed in detail the importance and pitfalls of advanced echo modalities such as strain technology and 3D echocardiography for the analysis of left atrial mechanics.

Strain imaging [1] seems to be the most promising technology for the direct evaluation of left atrial function [2]. However, the lack of dedicated software, standards for acquisition, and analysis limit the use of this technique.

P. Kuchynka et al. reviewed the role of cardiac magnetic resonance and computed tomography in assessment of left atrial size and function, especially before and after atrial fibrillation ablation.

Cardiac magnetic resonance is considered to be the gold standard for volumetric assessment of left atrial size. However, the cost and the availability of the technique do not seem to justify the potential added role when compared to 2D and 3D echo. Late gadolinium enhancement has the ability to tissue-characterize the atria and this may be used for optimizing the treatment of patients suffering from atrial fibrillation. However, the very promising results obtained by strain imaging in detecting atrial fibrosis may represent a valid alternative. Cardiac CT is considered the method of choice for evaluation of pulmonary vein and left atrial anatomy before catheter ablation procedures for atrial fibrillation and for detection of pulmonary vein stenosis after ablation. However, the exposition to ionizing radiations should be carefully taken into account.

D. Regazzoli et al. presented a comprehensive analysis of the potential role of left atrial appendage occlusion in stroke prevention. The left atrial appendage is considered the "most lethal human appendage" as it may cause significant mortality and morbidity in AF patients. In this regard, left atrial appendage occlusion could be an interesting and effective procedure in thromboembolism prevention in atrial fibrillation especially in certain categories of patients.

It is of note that G. de Maat et al. in the present issue demonstrated the effect of left atrial appendage amputation on atrial mechanics.

Finally, C. Santosa et al. presented data on the potential utility of combined 3D left atrial volume measurement and peak E wave mitral flow velocity as echocardiographic guides for acute volume resuscitation.

Taken together, the papers in this special issue present the recent developments and future perspectives in the morphological and functional evaluation of the atria and new possible therapeutic approaches. Importantly, these papers also unmask many challenging issues that should be overcome to improve the evaluation of atrial function as well as the new proposed therapeutical approaches.

Giovanni Di Salvo

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Clinical Study

The Utility of 3D Left Atrial Volume and Mitral Flow Velocities as Guides for Acute Volume Resuscitation

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Left ventricular end-diastolic pressure (LVEDP) is the foundation of cardiac function assessment. Because of difficulties and risks associated with its direct measurement, correlates of LVEDP derived by pulmonary artery (PA) catheterization or transesophageal echocardiography (TEE) are commonly adopted. TEE has the advantage of being less invasive; however TEE-based estimation of LVEDP using correlates such as left ventricular end-diastolic volume (LVEDV) has technical difficulties that limit its clinical usefulness. Using intraoperative acute normovolemic hemodilution (ANH) as a controlled hemorrhagic model, we examined various mitral flow parameters and three-dimensional reconstructions of left atrial volume as surrogates of LVEDP. Our results demonstrate that peak E wave velocity and left atrial end-diastolic volume (LAEDV) correlated with known changes in intravascular volume associated with ANH. Although left atrial volumetric analysis was done offline in our study, recent advances in echocardiographic software may allow for continuous display and real-time calculation of LAEDV. Along with the ease and reproducibility of acquiring Doppler images of flow across the mitral valve, these two correlates of LVEDP may justify a more widespread use of TEE to optimize intraoperative fluid management. The clinical applicability of peak E wave velocity and LAEDV still needs to be validated during uncontrolled resuscitation.

1. Introduction

Blood flow across the mitral valve reflects the instantaneous pressure difference between the left atrium and left ventricle. The pattern of flow is modified by left ventricular diastolic function [1]. Consequently, following the initial descriptions [2], two clinical applications of mitral flow measurements have been investigated: noninvasive calculations of intracardiac pressures [3, 4] and characterization of left ventricular diastolic function [5, 6]. Although the majority of the published literature has focused on these pressure and function assessments as monitors and guides for chronic therapy or as predictors of long term outcomes, they may also have utility during acute patient management, guiding optimization of intravascular volume [7, 8].

Transthoracic and transesophageal echocardiography (TEE) are used with increasing frequency to evaluate and monitor cardiac function in the perioperative setting. The diagnosis and management of the patient with hemodynamic instability are a level 1 indication for intraoperative TEE [9]. In addition, there is growing evidence that optimization of intraoperative cardiac function is associated with a decreased incidence of postoperative complications and shorter lengths of hospital stay [10]. The foundation of cardiac function assessment is left ventricular end-diastolic pressure (LVEDP) measurement. However, because of difficulties and risks associated with direct measurement of LVEDP, many correlates are used, ranging from pulmonary arterial catheter pressure measurements to less invasive TEE-based calculations. Mitral flow measurements form the basis of these TEE assessments. Additional measurements of tissue Doppler [11], pulmonary venous flow [12], color m-mode Doppler [1], or left atrial volume [13] can be incorporated to improve the accuracy of pressure calculations or left ventricular functional characterizations [14], but this increasing complexity may decrease its clinical utility, especially in the acute care setting.

For acute patient management, the most common TEE characterization of ventricular function is the left ventricular end-diastolic volume (LVEDV) [9, 15]. Although it has been shown to be quite sensitive to changes of intravascular volume [16], its use in this setting is limited by difficulties obtaining the most commonly used transgastric short axis image, the potential for regional wall motion abnormalities (RWMA) to produce misleading measurements, and the length of time required to measure LVEDV. In contrast, pulsed wave Doppler assessment of mitral flow is an image that can be obtained reliably and is amenable to rapid quantitative measurements [17]. Also, in contrast to left ventricular assessments, left atrial images are easily and reliably obtained, dynamic changes are not skewed by RWMA, and area measurements can be rapidly obtained using automated border detection algorithms. The potential applications of these additional echocardiographic measurements to guide acute resuscitation or volume optimization have not been extensively evaluated [8]. Using intraoperative acute normovolemic hemodilution (ANH) as a controlled hemorrhagic model we explored the potential utility of mitral flow and left atrial volume as markers of known changes in intravascular volume.

2. Methods

These data were collected as part of a single center, prospective, nonrandomized, observational study recruiting from consecutive patients scheduled for elective open prostatectomy, cystectomy, cystoprostatectomy, or anterior/posterior spinal fusion procedures that included ANH as a routine part of the perioperative strategy to minimize the need for homologous blood transfusion. Other results from this protocol have been previously reported [18].

After approval by the University of California Davis Human Subjects Research Committee, all patients provided written, informed consent prior to enrollment. Patients were excluded from consideration if there were contraindications to ANH or esophageal pathology that increased the risks associated with the placement of an ultrasound probe. All patients received preoperative intravenous sedative (midazolam 0.01–0.02 mg/kg). Upon arrival in the operating room, they were preoxygenated and standard physiological monitors were applied. All urological surgical patients received a single intrathecal injection of morphine (0.3 mg). Intravenous fentanyl (1–3 mcg/kg) and propofol (2-3 mg/kg) were then administered to induce general anesthesia. Neuromuscular blockade was established with rocuronium (1 mg/kg) to facilitate endotracheal intubation and provide muscle relaxation during surgery. General anesthesia was maintained with sevoflurane in an air/oxygen mixture to achieve a fractional inspired oxygen concentration of 0.6. Normocapnia was maintained with tidal volumes averaging 8 mL/kg and a positive end-expiratory pressure of 5 cm H_2O. A radial arterial catheter was then placed, large bore peripheral venous access was established, and the stomach was suctioned with an 18Fr orogastric tube to enhance image acquisition prior to insertion of the TEE probe (V5M probe, Siemens Sequoia Cardiovascular System Model #C512, Siemens Medical Solutions, Malvern, PA).

After a stable anesthetic state had been established, baseline hemodynamic parameters were recorded along with the TEE images described below. The acute normovolemic hemodilution protocol was then initiated. Total blood volume was estimated using the standard formula of 70 mL/kg for male and 65 mL/kg for female patients. Blood removal was accomplished via the peripheral venous catheter with the use of a tourniquet or via the arterial line. 15% of the estimated blood volume (EBV) was removed in three separate aliquots, each one 5% of the EBV. Each aliquot was withdrawn over approximately 10 minutes, during which time the patient's vital signs were continuously monitored to ensure tolerance to this controlled hemorrhage. Blood was collected in standard citrate phosphate dextrose solution blood packs (Baxter Healthcare Corp., Deerfield, IL), agitated to prevent clotting, marked with the patient's information, and kept in the operating room at room temperature until it was reinfused after complete surgical hemostasis. After a total of 15% of the EBV had been removed, the intravascular volume was then replaced, also in three 5% of the EBV aliquots, using an equal volume of 6% hetastarch in lactated electrolyte solution (Hextend, Hospira, Inc., Lake Forest, IL). All hemodynamic measurements and TEE recordings were repeated after each 5% EBV aliquot removal and replacement. The time to complete the ANH and data collection averaged approximately 1 hour. Seven study points were thus defined by this protocol (baseline, EBV −5%, −10%, and −15%, hemodilution to −10% EBV, −5% EBV, and original EBV). If a patient became hemodynamically unstable at any time during the blood removal or replacement (greater than 15% drop in the mean arterial pressure (MAP)) a phenylephrine bolus of 0.1 mg was given. If the hypotension did not resolve, a phenylephrine infusion was started and titrated to maintain the MAP ≥ 50 mmHg. The infusion was tapered and stopped when the MAP was ≥60 mmHg. Physiologic measurements were recorded at least five minutes after a phenylephrine bolus or change in the infusion rate. Two anesthesia care teams were involved in the study; one was solely focused on the patient's care and the other was responsible for data collection.

For each study point defined above, the long axis view of the left ventricle was obtained with the TEE probe positioned in the mid-esophageal four-chamber (ME 4CH) view. Care was taken to optimize LV chamber size and avoid foreshortening. The probe was then rotated to position the left atria and ventricle in the center of the imaging plane. Three-dimensional software was then used to acquire a series of EKG-gated images spanning a 180° rotation of the transducer at 5° intervals (total of 36 images). These images were then stored for offline 3D reconstruction and assessment of left atrium end-diastolic volume, end systolic volume, and ejection fraction using proprietary software *four*Sight (Research Arena, TomTec Imaging Systems, Unterschleissheim, Germany). For these volumetric measurements, the endocardial border was traced in four equally spaced orthogonal pairs of images selected from the 3D reconstruction, that is, each one twenty-two and one-half degrees from the previous measurement. TEE image acquisition was supervised by an anesthesiologist board certified in advanced perioperative

Table 1: Average values for left atrial volume and mitral flow measurements.

Study point	Baseline	EBV-5%	EBV-10%	EBV-15%	Hemodilution to −10%	Hemodilution to −5%	Restored EBV
LAEDV (cm^3)	47 ± 13.7	48 ± 15.5	**44 ± 16.6***	43 ± 15.4	49 ± 17.0	52 ± 15.3	**55 ± 19.2***
Peak E (s)	0.61 ± 0.146	**0.57 ± 0.142***	**0.54 ± 0.115***	0.53 ± 0.155	0.64 ± 0.153	0.66 ± 0.185	**0.72 ± 0.156***
Peak A (s)	0.48 ± 0.163	0.43 ± 0.138	0.42 ± 0.146	0.44 ± 0.148	0.47 ± 0.138	0.47 ± 0.141	0.53 ± 0.191
E/A ratio	1.3 ± 0.33	1.4 ± 0.39	1.4 ± 0.44	1.3 ± 0.44	1.3 ± 0.38	1.4 ± 0.38	1.4 ± 0.43
E decel (ms)	152 ± 60.9	165 ± 60.2	180 ± 72.0	150 ± 58.8	167 ± 60.6	168 ± 50.9	160 ± 50.8
A decel (ms)	114 ± 46.6	124 ± 51.5	114 ± 46.4	113 ± 38.5	133 ± 60.0	120 ± 49.0	115 ± 31.3
E VTI (cm)	0.12 ± 0.106	0.10 ± 0.035	0.11 ± 0.091	0.11 ± 0.129	0.11 ± 0.034	0.12 ± 0.035	0.12 ± 0.038
A VTI (cm)	0.06 ± 0.026	0.06 ± 0.028	0.08 ± 0.126	0.06 ± 0.026	0.07 ± 0.041	0.07 ± 0.039	0.07 ± 0.030

All values are mean ± SD. $^*P < 0.05$ versus baseline. LAEDV: left atrial end-diastolic volume, Peak E: peak E wave velocity, Peak A: peak A wave velocity, E decel: E wave deceleration time, A decel: A wave deceleration time, E VTI: E wave velocity time integral, and A VTI: A wave velocity time integral.

TEE and, for consistency, all of the left atrial volumetric analyses were performed by one researcher.

With the TEE probe in the same ME 4CH position, color flow Doppler imaging was used to detect any significant mitral valvular disease. Transmitral flow was then assessed using pulsed wave Doppler with the sample window placed at the tip of the mitral leaflets. After the transmitral flow image was optimized, a still image store was recorded for subsequent measurements of peak E wave amplitude, peak A wave amplitude, E/A ratio, E wave deceleration time, A wave deceleration time, and velocity-time integrals (VTI) for both waves.

Unless noted, all values are presented as mean ± SD. For measurements repeated over time, a one-way ANOVA was used with Dunnett's multiple comparison test to determine statistically significant differences compared to baseline across the seven conditions of graded blood removal and replacement (GraphPad Prism, ver. 6.05, GraphPad Software, San Diego, CA). For all comparisons, a P value of <0.05 was considered statistically significant.

3. Results

A total of 48 patients were consented for this protocol, all of whom were either ASA I or ASA II. No one was eliminated from the study due to intolerance of the hemodilution. However, a total of seven patients were dropped from analysis: two due to a change in the surgical procedure, one due to the loss of venous access, and four due to the TEE machine not being available. Of the remaining 41 patients, 36 had images of sufficient quality for volumetric analysis. This group included 31 males and 5 females. Their average age was 59 ± 6.4 years, weight 90 ± 14.4 kg, height 174 ± 9.5 cm, and BMI 29 ± 4.4. Surgical procedures included 26 prostatectomies, 4 cystectomies or cystoprostatectomies, and 6 anterior/posterior spinal fusions. Mitral flow data was attempted in 32 patients. All of these patients had images of adequate quality for analysis. This group included 26 males and 6 females. Their average age was 58 ± 6.6 years, weight 85 ± 13.4 kg, height 174 ± 8.8 cm, and BMI 28 ± 4.5. Surgical procedures included 26 prostatectomies, 5 cystectomies or cystoprostatectomies, and 5 anterior/posterior spinal fusions.

No clinically significant changes in heart rate or blood pressure were observed during the ANH protocol (Figure 1). The measurements of left atrial volume and mitral flow parameters during each of the seven measurement points are collated in Table 1. Only the LAEDV and peak E wave velocity demonstrated statistically significant changes that correlated with the known changes in intravascular volume associated with ANH. At the −15% of EBV time point the LAEDV was −10 ± 21.4% of the baseline value while the peak E wave velocity was −9 ± 25.4% of baseline (Figure 2). Similar changes were also seen at the final study point when the EBV had been restored with Hextend. LAEDV actually overcorrected to 20 ± 37.5% greater than baseline and the peak E wave velocity similarly increased to 19 ± 22.8% greater than baseline.

4. Discussion

Acute volume resuscitation and optimization of intracardiac pressures (preload) are a dynamic situation best guided by continuous monitors of cardiac function. The pulmonary arterial (PA) catheter has historically been considered the gold standard in this setting, but it is used with decreasing frequency due to the limits of the information it provides and the risks and complications associated with its placement and use [19]. Central venous pressure monitoring is sometimes used as an alternative, but its placement is associated with similar risks and complications and the clinical utility of the information provided is limited, at best [20]. Transesophageal echocardiography presents an alternative continuous, real-time monitoring option for cardiac function. When compared to the pulmonary arterial catheter it is less invasive with fewer associated risks and complications.

In the clinical setting of acute volume resuscitation, the goal is to optimize the preload of the left ventricle (LVEDP) to maximize cardiac function as guided by the Frank-Starling relationship between LVEDP and cardiac output. The PA catheter uses PCWP as a surrogate for LVEDP, but correlations may be limited by left atrial or mitral valvular pathology. In contrast, the TEE uses the left ventricular end-diastolic volume (LVEDV) as a more direct surrogate for LVEDP and is now a commonly used monitor for this application [9].

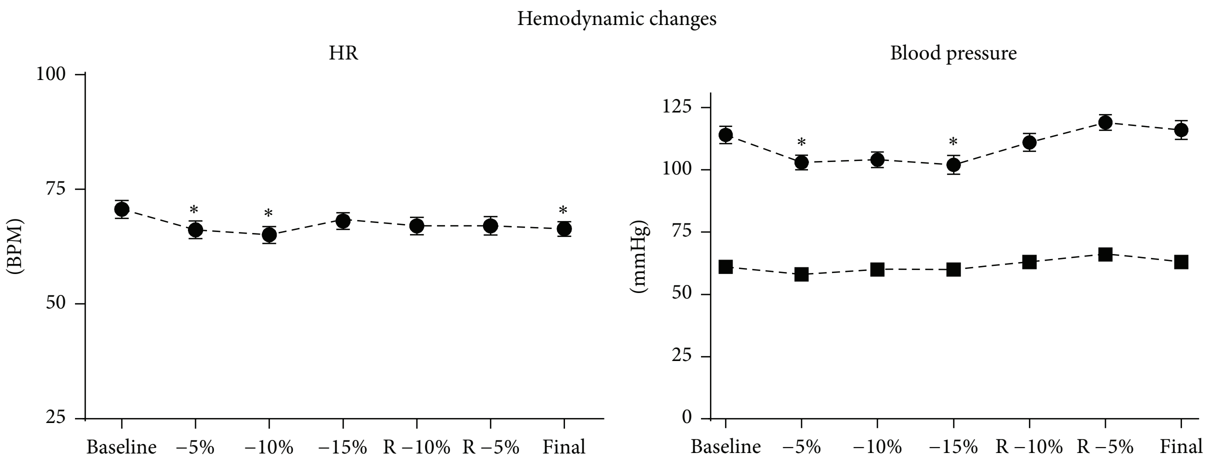

Figure 1: Hemodynamic changes; “∗” indicates $P < 0.05$ versus baseline.

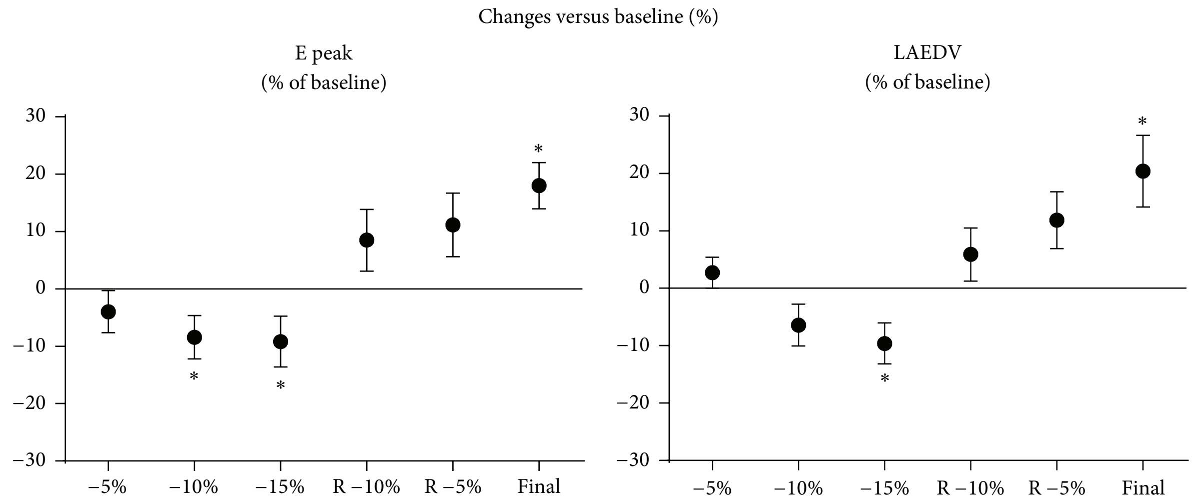

Figure 2: Changes versus baseline (%); “∗” indicates $P < 0.05$ versus baseline, E Peak: peak E wave velocity, LAEDV: left atrial end-diastolic volume.

It has been demonstrated to be a sensitive measure, responding to changes as small as 2.5% of the intravascular volume [16], and the accumulated data in support of its use makes it one of the few level 1 indications for intraoperative TEE [9]. However, there are limits. Image acquisition can sometimes be difficult. If a transgastric sort axis view is used, RWMA can lead to misleading assessments. More comprehensive characterizations can be obtained using orthogonal mid-esophageal LV long axis views, but for these, as well as the transgastric short axis images, quantification of LVEDV can be tedious, leaving subjective assessments as the most common guide, despite the critical nature of this clinical setting. A monitor that could provide more easily obtained quantitative measurements would be beneficial and decrease the requirements for clinical experience in the assessment of clinical changes during this dynamic period.

TEE can also be used to indirectly calculate the LVEDP. Shortly following the initial description of Doppler measurement of mitral flows by Kitabatake et al. [2], the potential use of these values to calculate LVEDP was demonstrated. Subsequent studies have shown improved accuracy of these calculations when tissue Doppler [11], pulmonary venous flow [12], color m-mode Doppler [1], and 2D left atrial volume [13] measurements are also considered [1]. Unfortunately, as a result, the calculations become too complex to be of much use in the acute clinical setting [1, 12, 13]. The majority of investigations of mitral flow patterns and left atrial volume measurements have focused on using this information to characterize the left ventricular diastolic function as a predictor of long term outcomes or monitor of chronic heart failure therapies [5, 6].

The results of this study demonstrate the potential utility of mitral flow patterns as guides in the acute care setting.

In contrast to the transgastric short axis view of the left ventricle, Doppler flow images across the mitral valve are easily and reliably obtained even in critically ill patients [17]. The measurement point at the tip of the mitral leaflets is standardized and reliably reproduced and the flow patterns are easily quantitated. Our results support a single measurement of the peak E wave velocity for this application. Furthermore, just as measurements of the left atrial volume can increase the predictive value of mitral flow patterns regarding long term outcomes, our results indicate that acute changes in left atrial volume may also be used to guide acute resuscitation. Left atrial images are similarly easy to obtain and the more distinct tissue boundaries make them easily quantified.

This study has some limitations that should be highlighted. First, these left atrial volume calculations were done offline using very early versions of the analytical software. Increasing computing capabilities have supported the evolution of TEE imaging options. The initial characterizations of left atrial volume applied Simpson's method of discs to biplanar images, despite the known inaccurate geometric assumptions. Three-dimensional imaging has become routine and provides particular advantages when applied to the irregular shape of the left atrium. Similarly, advances in echocardiographic edge detection software [21] combined with programs designed specifically for the left atrium [22] have been shown to correlate well with other volumetric imaging modalities and make a continuous display of left atrial volume possible. The utility of this more current software should be evaluated with respect to this and similar clinical applications. A second limitation to be considered is the potential for incomplete visualization of the left atrium because of the smaller offset between the esophagus and the left atrium. There are often shoulder areas that extend beyond even the widest possible sector scanning angles. Without the use of a device that could manipulate this offset distance, it is not possible to calculate exactly how much of the left atrium is not visualized and measured; however, our results suggest that this is a relatively small percentage of the total atrial volume. Furthermore, when used in a clinical setting, comparisons would necessarily be made with the baseline values for that patient rather than to a standard "normal" value, further decreasing the impact of any incomplete volume measurements. The potential advantages of this measurement still appear to outweigh the disadvantages associated with left ventricular measurements. A final limitation that should be highlighted is that despite the substantial changes in intravascular volume associated with this ANH protocol, they occurred in a controlled and predictable fashion. A prospective evaluation of these findings in a less controlled resuscitation combined with assessments of cardiac function and clinical outcomes is still required.

5. Conclusions

The use of ANH as a controlled human hemorrhagic model allowed the demonstration of the potential utility of 3D left atrial volume measurements and peak E wave mitral flow velocity as echocardiographic monitors that may be used as guides for acute volume resuscitation. Further evaluation in other clinical scenarios is merited.

Conflict of Interests

None of the authors on this paper have any possible conflict of interests associated with this work including secondary interests such as financial gain.

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Review Article

The Role of Magnetic Resonance Imaging and Cardiac Computed Tomography in the Assessment of Left Atrial Anatomy, Size, and Function

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In the last decade, there has been increasing evidence that comprehensive evaluation of the left atrium is of utmost importance. Numerous studies have clearly demonstrated the prognostic value of left atrial volume for long-term outcome. Furthermore, advances in catheter ablation procedures used for the treatment of drug-refractory atrial fibrillation require the need for detailed knowledge of left atrial and pulmonary venous morphology as well of atrial wall characteristics. This review article discusses the role of cardiac magnetic resonance and computed tomography in assessment of left atrial size, its normal and abnormal morphology, and function. Special interest is paid to the utility of these rapidly involving noninvasive imaging methods before and after atrial fibrillation ablation.

1. Introduction

In recent years there has been increased interest in the comprehensive evaluation of the left atrium (LA). The main role of the LA is to modulate left ventricular (LV) filling through several mechanical functions: reservoir function, conduit function, and active contraction [1]. Preserved active LA pump function contributes up to 30% of the total LV stroke volume; its loss due to atrial fibrillation or ventricular pacing may lead to symptomatic deterioration, especially in the setting of LV dysfunction [2]. Left atrial size increases for a number of reasons: due to pressure overload caused by LV filling pressures or mitral stenosis; due to volume overload associated with mitral regurgitation or high cardiac output; or due to atrial fibrillation (AF). Dilatation of the LA has been repeatedly shown to be a strong marker of adverse cardiovascular outcomes [3–6]. The introduction of catheter ablation techniques for the treatment of drug-resistant AF has represented an important stimulus for advances in the field of multimodality imaging of the LA.

The aim of this paper is to give a detailed overview on the utility of cardiac magnetic resonance (CMR) and cardiac computed tomography (CT) in the assessment of LA anatomy, size, and function.

2. Cardiac Magnetic Resonance

2.1. Basic Aspects of Cardiac Magnetic Resonance Imaging. Cardiac magnetic resonance has been considered the gold standard for assessment of the heart chambers [7]. Its high spatial and temporal resolution allows accurate assessment of the morphology and function of both the atria and ventricles in healthy subjects as well as in patients with various structural heart diseases. The advantage of CMR is the absence of radiation exposure and the ability to characterize tissue composition. Cine CMR images are obtained as end-expiratory breath-hold and ECG-triggered acquisitions with steady-state free precession sequences. Consecutive multi-slice acquisitions of the entire LA in short-axis view with either manual tracing of the atrial wall or automated border detection form basis for the assessment of LA volumes based on Simpson's method of discs (Figure 1). Slice thickness is usually between 2.5 and 5 mm, with a temporal resolution of 25 to 50 ms. Alternatively, LA volumes may be measured using the biplane area-length method in the horizontal and vertical long axes [8]. Left atrial area shall be measured in four-chamber view (Figure 2). The uniqueness of CMR as compared to echocardiography as well as cardiac CT is its ability of tissue characterization and scar imaging using late gadolinium enhancement (LGE) technique [8]. Inversion recovery gradient echo sequences in long and short axes are acquired 10–20 minutes after the injection of gadolinium-based contrast agent. Gadolinium-enhanced three-dimensional magnetic resonance angiography provides detailed information on pulmonary vein anatomy in relation to the LA cavity (Figure 3). If contrast agent administration is contraindicated, three-dimensional steady-state free precession angiography may be a viable option for how to assess anatomy of pulmonary veins and the LA.

The main limitations of CMR examination are the length of the complete heart imaging procedure (about 45 minutes), the financial burden, possible evocation of claustrophobia, limited availability, and the incompatibility of certain prosthetic materials [9]. Furthermore, gadolinium-containing contrast agents are contraindicated in subjects with glomerular filtration rate $< 30\,\mathrm{mL/min/1.73\,m^2}$ due to the risk of developing nephrogenic systemic sclerosis.

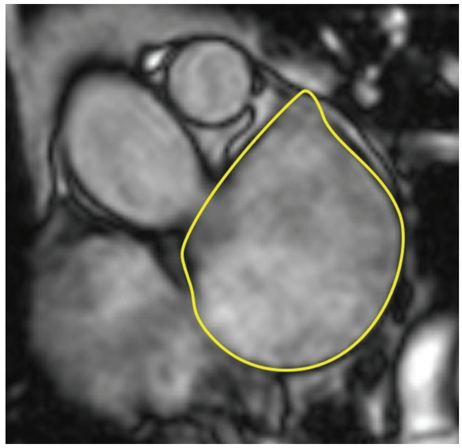


Figure 1: Representative slice demonstrating the tracing of the left atrial boundary at ventricular end-systole in short-axis view on steady-state free precession magnetic resonance image. The left atrial volume is then calculated using the disk area summation method (Simpson's method) from contiguous slices covering the whole left atrial cavity.

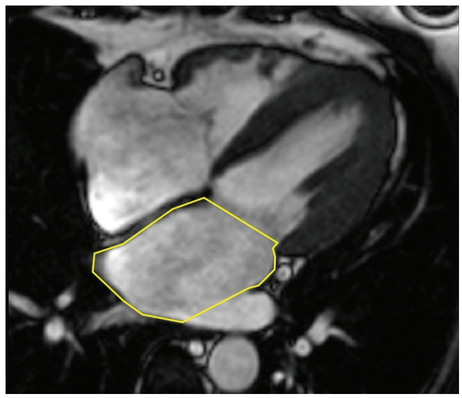


Figure 2: Measurement of the left atrial area at ventricular-end systole in four-chamber view on steady-state free precession magnetic resonance image.

2.2. Left Atrial Morphology. Accurate visualization of LA morphology is essential in many clinical situations, such as assessment of the feasibility of radiofrequency ablation (RFA) in patients with atrial fibrillation (AF), planning cardiovascular surgery, evaluation of left atrial appendage (LAA) thrombosis, and evaluation of various other pathological masses like tumours and infiltration of the cardiac wall. Conventionally, transthoracic echocardiography (TTE) has been the most useful and practical method for atrial investigation in daily clinical practice due to its wide availability and cost-benefit ratio. Cardiac CT currently represents a gold standard for assessment of the anatomy of the LA complex, LAA shapes and lobes, LA wall thickness, atrial septal anomalies such as septal defects, patent foramen ovale, and diverticula. Cardiac CT is generally performed rapidly, with acceptable temporal resolution and high spatial resolution. Nevertheless, standard CMR techniques also allow assessment of some LA morphological and functional parameters with reasonable accuracy which may be of particular importance in patients undergoing RFA of atrial fibrillation as described in more detail below.

2.3. Left Atrial Masses. Cardiac magnetic resonance allows excellent characterization of various intra-atrial masses. The technique enables superior tissue characterisation and thus differentiation between cardiac tumours and thrombi. Cardiac magnetic resonance can also be helpful in differentiating between benign and malignant tumours. In a study comprising 116 patients with various cardiac masses, Pazos-López et al. used CMR to show that tumours tend to be larger, heterogeneous, and more mobile compared to thrombi [10]. The presence of LGE and hyperintensity on T2-weighted images is also typical for tumours rather than for thrombi. However, the accuracy of CMR in distinguishing between benign and malignant tumors was moderate in this study. Malignant tumours were larger and exhibited contrast first-pass perfusion and the presence of LGE more frequently. Myxomas represent the most common benign tumours in LA, followed by rhabdomyomas and fibromas. Myxomas are typically mobile, oval masses attached to the atrial septum, and they tend to have heterogeneous CMR signal with a typical LGE pattern [10, 11]. Less frequent LA mass findings include malignant tumours such as lymphomas and

Figure 3: Normal anatomy of four pulmonary veins (red stars) on three-dimensional contrast-enhanced magnetic resonance angiography.

sarcomas, and nonneoplastic lesions like thrombi, infectious vegetations, and pericardial cysts [11].

2.4. Left Atrial Size. Increased LA size has been shown to be a marker of LV diastolic dysfunction as well as a predictor of conditions like myocardial infarction, heart failure, stroke, and atrial fibrillation [12–15]. In the past, LA diameters and areas were the key measured LA parameters. However, LA volume has been demonstrated to be a more robust marker of cardiovascular events [6]. Interestingly, recent literature has provided growing evidence that minimal rather than maximal LA volume should be the focus of research, as minimal LA volume better reflects LV diastolic pressure and predicts elevated pulmonary wedge pressure more accurately than maximal LA volume [16–18].

The standard evaluation of LA size in daily clinical practice is performed by transthoracic echocardiography. However, echocardiographic assessment is often inaccurate due to geometric assumptions and foreshortening of the LA cavity [18]. The accuracy of CMR volumetric measurements has been demonstrated via the tight correlation between CMR and cadaveric casts and with other imaging methods [9, 19]. Agner et al. performed an interesting head-to-head comparison of TTE, CCT, and CMR in the assessment of LA volume and function in patients with atrial fibrillation. The results of this study showed that TTE tends to underestimate the LA maximal and minimal volumes, while CT overestimates maximal and minimal LA volumes compared to CMR [20].

The current European heart failure guidelines recommend assessment of LA volume in all patients with heart failure regardless of the aetiology [21]. CMR is not a routine imaging modality for this assessment due to time and financial considerations. However, several studies have shown excellent correlation between LA CMR measurements and cardiovascular outcomes. Gulati et al. demonstrated a strong association between LA volume measured by CMR with transplant-free survival and heart failure outcomes in 483 patients with dilated cardiomyopathy [22]. Individuals with dilated cardiomyopathy with an indexed LA volume more than 72 mL/m^2 had a threefold higher risk of death or transplantation compared to those with an indexed LA volume less than 72 mL/m^2 [22]. In another study Jahnke et al. demonstrated that LA volumetry based on cine imaging predicted the success of pulmonary vein isolation for AF. An LA diastolic (i.e., maximal) volume of less than 112 mL was associated with sustained sinus rhythm following RFA with 80% sensitivity and 70% specificity [23].

Established CMR reference values of LA parameters are based on data derived from several studies [1, 7, 24, 25]. The normal LA volume is defined as 97 ± 27 mL with gender-specific values of 103 ± 30 mL for males and 89 ± 21 mL for females. The upper limit of LA area measured in the four-chamber view is 23 cm^2 [26].

The MESA (Multi-Ethnic Study of Atherosclerosis) demonstrated that LA enlargement and deterioration of LA function precede the development of heart failure [27]. In this study, 112 participants with incident heart failure and 224 controls matched for sex and age were followed for 8 years. Left atrial volume and function were assessed by CMR feature-tracking. The results showed that global peak longitudinal atrial strain and higher LA minimal volume were independent markers of incident heart failure in a multiethnic population of asymptomatic individuals.

However, all these data raise an intriguing question regarding the need for highly accurate measurement of LA size [18]. For example, it is not known whether the LA appendage, which is included in the volumetric measurement by CMR but not by echocardiography, meaningfully contributes to LA volume, especially in patients with high LA volumes [18].

2.5. Left Atrial Function. Cardiac magnetic resonance assessment of LA function is currently not used in routine practice, but it has been attracting more research attention due to the technical development of imaging methods. The technique is highly suitable for studying parameters like LA phasic volumes and emptying fractions (total, passive, and active). Although not as high as in 2D echocardiography, the temporal resolution of steady-state free precession sequences of 25 to 50 ms is sufficient for the evaluation of LA volumes during cardiac cycle. It was demonstrated that LA passive volumetric contribution to LV filling decreases with age, while its active component increases with age. These age-related differences are augmented by dobutamine challenge, as shown by Ahtarovski et al. [28].

In a study of 210 subjects with a history of long-lasting arterial hypertension, Kaminski et al. proved a strong association between decreased LA contractile function and patient mortality, nonfatal events, and all major adverse cardiovascular events (MACE) [29]. Every 10% reduction of LA contractile function increased the risk of death, nonfatal event, or MACE by 1.5-, 1.4-, and 1.8-fold, respectively. According to multivariable analyses, the active LA contribution to LV filling was the strongest predictor of MACE.

Quite recently, Kowallick et al. reported results from a small study assessing LA deformation by CMR myocardial feature tracking. In this study 10 patients with hypertrophic cardiomyopathy, 10 individuals with heart failure with preserved LV ejection fraction, and 10 healthy volunteers were studied using CMR assessment of LA longitudinal strain and strain rate parameters derived from steady-state free precession cine images. The results showed reliable quantification of LA conduit, reservoir, and contractile function both in disease states and in healthy individuals. Moreover, excellent intra- and interobserver agreement was noted [30]. This novel approach to LA function assessment seems promising; however, larger studies on this topic need to be conducted in the future.

2.6. Radiofrequency Ablation of Atrial Fibrillation. Detailed assessment of the LA by CMR is increasingly used in the field of atrial arrhythmias, particularly AF. It is well known that episodes of paroxysmal AF are triggered by an ectopic beat in the muscular layer of the pulmonary veins in more than 90% of cases [31]. Further abnormal activation of the atrium is then influenced by pathological changes within the atrial wall, which shares many similarities with the pulmonary veins due to their common embryogenic development from the primitive common pulmonary vein [32].

Radiofrequency ablation of both paroxysmal and persistent AF has been performed with increasing frequency since 2003 [33]. This method is based on electrical isolation of the pulmonary veins and further ablation in LA causing linear isolations within the atrial roof and left isthmus. However, the success rate of this procedure, particularly in cases of persistent AF, is rather disappointing, with only about 57% of patients remaining in sinus rhythm after the first procedure and 71% after multiple procedures [34]. The complication rate of RFA reaches 5%, comprising mainly pulmonary vein stenosis (2–5%), tamponade (1.2%), atrioesophageal fistulas (0.05%), phrenic nerve injury, and bleeding [35]. Various imaging modalities, such as intracardiac echocardiography, cardiac CT, and CMR, can be applied to optimize the entire procedure. Cardiac CT is the most widely used method for individually tailored management of AF by sophisticated visualization of the LA in a simple and rapid manner. Nevertheless, CMR also has the potential to be used in all phases of RFA—before procedure, in real time during the procedure, and after procedure. However, its role is still experimental and research-based.

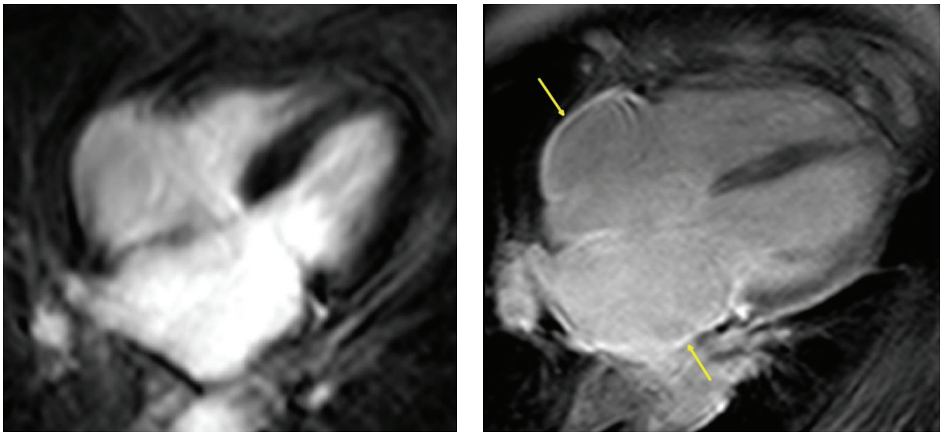
Preprocedural CMR images of the LA help to identify the anatomical relationship of the LA to other structures in thorax, thus enabling easier orientation within the LA for RFA operators. The location of the oesophagus is highly variable due to its peristaltic activity, but most often it lies directly behind the LA, very close to the left pulmonary veins, posing the risk of creating an atrial-esophageal fistula with possibly catastrophic consequences. Meng et al. showed that one-third of patients treated with RFA had oesophageal LGE on CMR performed 2 months following the ablation procedure [36]. The occurrence of LGE was not related to ablation time, type of catheter, oesophageal location, or LA size. The clinical significance of these findings is unknown; however, the LGE might represent scar tissue, with risk for delayed perforation.

The presence of thrombus in the LA appendage represents an absolute contraindication for RFA. Transoesophageal echo (TOE) is the standard method for excluding the presence of thrombus in the LA appendage with high negative predictive value (96–100%) [37]. However, TOE cannot be performed in some patients for various reasons, and CMR may represent a viable option for the exclusion of intra-atrial thrombosis. Ohyama et al. studied 50 patients with chronic nonrheumatic AF and a history of stroke who underwent both TOE and CMR. In the study, thrombosis was detected by CMR in three patients who were declared thrombus-free by TOE [38]. This finding might be either due to the higher sensitivity of CMR compared to TOE or due to its lower specificity caused by respiratory motion artefacts during CMR. Furthermore, a significant correlation has been demonstrated between CMR and TOE measurements of peak emptying velocity of the LA atrial appendage, which is a predictor of thrombus formation [37].

Preprocedural identification of pulmonary vein anomalies—their number, location, or branching–could potentially decrease the recurrence rate of AF and the risk of pulmonary vein stenosis. Pulmonary vein stenosis occurs in about 2–5% of patients undergoing RFA [39]. It is caused by intimal proliferation and myocardial necrosis induced by radiofrequency energy. Stenotic lesions are more likely to develop in smaller veins after extensive ablation performed deeper in the pulmonary vein trunk [40, 41]. Pulmonary vein stenosis may be completely asymptomatic or it can lead to pulmonary hypertension and hypoperfusion of the affected lung segments, manifesting with cough and dyspnoea [39]. Pulmonary vein angioplasty is usually sufficient to relieve patients' symptoms and it is required in about 50% of cases [42]. Although CMR as well as CT is able to visualize pulmonary vein stenosis with high accuracy, TOE is usually the first method performed when suspicion for this postprocedural complication is raised due to its wide availability and lack of radiation.

Variation in pulmonary vein anatomy occurs in approximately 40% of patients indicated to the ablation procedure [43]. Most often there is a single left common pulmonary vein or an additional right middle pulmonary vein. Right-sided pulmonary veins tend to form earlier than left-sided pulmonary veins during embryonic development and thus have more time to be incorporated into the LA, whereas left-sided pulmonary veins form later, leading to a higher frequency of a common trunk on the left side [39].

Surprisingly, several studies have failed to support the hypothesis that assessment of pulmonary vein number, location, and branching prior to RFA affects long-term efficacy of RFA [44–46]. The only parameters predictive of AF recurrence seem to be the diameter of the pulmonary ostia, particularly their cross-sectional area, and increased pulmonary vein contraction [47, 48]. The measurement of the pulmonary vein ostia is complicated, as there is no clear anatomical border between the pulmonary veins and the LA. The ostia are ovoid and their size varies during the cardiac cycle. Maximal diameter, perimeter, and cross-sectional area can be measured by CMR in the sagittal plane. In an important study conducted by Syed et al., measurements of pulmonary vein ostia were performed by CT, intracardiac echocardiography, TOE, and venography, resulting in different numbers and positions of pulmonary veins, with poor



(a) (b)

Figure 4: The examples of inversion recovery gradient echo sequencies in four-chamber view demonstrating the absence (left) and the presence of late gadolinium enhancement (right; arrows) in atrial walls.

correlation of diameter measurements among the imaging modalities [49]. Patients with the highest cross-sectional areas measured by CMR tend to have recurrent AF after ablation independently of the type of AF and LA size. Furthermore, it seems that preservation of pulmonary vein contraction on follow-up CMR might be an independent predictor of incomplete ablation [48].

Extensive structural remodelling of the LA seems to play an important role in the prediction of the phenotype of AF, recurrence of arrhythmia, thromboembolic events, and mortality [9]. Left atrial remodelling can be predicted using CMR by the severity of atrial enlargement and by the extent of LGE [9, 50]. Left atrial LGE results from altered washout kinetics of gadolinium from fibrotic regions relative to normal surrounding tissue (Figure 4) [51, 52].

A unique scoring system called The Utah Staging System has been developed to quantify the degree of LA structural remodelling based on the extent of LGE: Utah stage I is defined by less than 5% LGE, Utah stage II as 5–20% LGE, Utah stage III as 21–35% LGE, and Utah stage IV as more than 35% LGE [53]. A significant correlation between the extent of LGE and clinical outcome has been repeatedly demonstrated. In a study by Daccarett et al. the recurrence rate of AF within 8 months after RFA was 0% in patients with Utah stage I and 56% in Utah stage IV [50]. Another study by Oakes et al. documented AF recurrence after RFA in 14% of patients with minimal LGE of the LA wall, in 43.3% of patients with moderate LGE, and in 75% of patients with extensive LGE of the LA wall [53]. A high scar burden preablation thus predicts a high recurrence rate of AF, as well as increased difficulty and length of the ablation procedure. Oakes et al. also noticed a relationship between the location of scarring and the extent of LGE. Patients with mild to moderate LGE of the LA were particularly affected on the posterior LA wall and interatrial septum, while patients with extensive enhancement had scarring detectable in all parts of the LA wall. The same authors also showed a statistically significant correlation between LA volume and the extent of LGE [53].

Scarring of the LA wall visualized by LGE also seems to be associated with increased risk of thromboembolism. According to Wylie et al., this risk is related to the decreased contractile function of the LA, even in the absence of AF [54]. Daccarett et al. showed that patients with mild remodelling of the LA, defined as an extent of LGE less than 8.5%, experienced low rates of thromboembolic complications (LGE 2.8%). On the other hand, more than 50% of patients with severe enhancement (LGE >21.1%) experienced an ischemic event. Furthermore, a higher extent of scarring was noted in patients with a prior history of stroke compared to patients with no history of stroke [50].

Based on these findings, CMR could aid in the stratification of AF patients, allowing for optimal choice of treatment and individualized care. Patients with low grade LGE are likely to benefit from the standard ablation protocol, while patients with extensive LA fibrosis should probably be treated conservatively with adequate rate-control management with long-term anticoagulation or with an extensive ablation strategy (i.e., ablation of the posterior wall and septal LA debulking) [50, 53]. Nevertheless, it must be clearly stated that the evaluation of the presence and the extent of LGE in the LA wall is very difficult due to its thinness and requires a high expertise in CMR.

A further challenge is the use of real-time CMR for online navigation of the ablation catheter. The use of CMR could give the operator immediate feedback of lesion formation during ablation, thus distinguishing between true scar formation and tissue oedema that leads to a temporary electrical gap, with delayed pulmonary vein reconnection [37]. In addition, the use of CMR could reduce possible complications by allowing real-time monitoring of the catheter position in relation to the oesophagus, pericardium, and other structures. Real-time CMR has already been tested in experimental settings and new techniques are in development. However, its widespread use is unlikely at the present time.

Postablation CMR enables visualisation of LGE as a correlate of postablation scar formation, which is likely to be predictive of RFA success [55, 56]. According to McGann et al. individuals with minimal scar formation induced by RFA had a higher rate of AF recurrence at 3-month follow-up [55]. Another important marker of the success of the ablation procedure is the creation of a circumferential pulmonary vein scar. However, this may be achieved in only about 7% of patients undergoing RFA, as shown by Badger et al. [57]. Therefore, while preablation atrial scarring predicts a lower likelihood of successful RFA, the postablation visualisation of low LGE around the pulmonary vein ostia is predictive of AF recurrence and can be helpful in planning redo procedures.

The integration of data from electroanatomic mapping with CMR or cardiac CT images into so-called hybrid maps represents an intriguing application of CMR. However, the results of existing studies seem to be quite controversial. Bertaglia et al. described significantly improved outcomes of patients after RFA using merged CMR hybrid maps [58]. On the other hand, Kistler et al. did not corroborate these data in a study using combined electroanatomic mapping with morphological information provided by cardiac CT [59]. Similarly, Caponi et al. examined the use of hybrid CMR and electroanatomic mapping and also did not observe improved clinical outcomes in neither paroxysmal nor persistent AF [60]. The number of AF recurrences was similar in both groups after 12 months of follow-up. Although the use of CMR did reduce fluoroscopy time, it had no effect on procedural success or long-term efficacy [60]. Nevertheless, reduction of X-ray exposure is an important issue because many patients require repeated procedures associated with a high radiation dose, increasing their risk of malignancy.

3. Cardiac Computed Tomography

3.1. Basic Aspects of Cardiac Computed Tomography. Computed tomography imaging of the heart requires minimization of cardiac motion artefacts. For this reason, cardiac CT scanning is almost exclusively performed with simultaneous ECG registration. Two basic methods are recognized: prospective triggering and retrospective gating. Prospective ECG triggering is a method in which the data are acquired at a prespecified phase of the cardiac cycle (usually during the phase with minimal heart motion and therefore minimal coronary artery motion—thus in mid-diastole or in end-systole in patients with accelerated heart rate). In retrospective ECG gating, data are acquired throughout the entire cardiac cycle, and the only data obtained during the cardiac phase with the least motion artefacts are used for image reconstruction [61]. The protocol for cardiac CT is highly dependent on the technology delivered by each vendor. Some vendors attempt to decrease the radiation dose by prospective triggering and fast rotation times, while others build their protocols mainly on helical scanning and ECG pulsing, where full-dose images are acquired only during a preselected phase. Prospective ECG triggering is being performed more frequently in recent years because of its relatively low radiation dose in comparison with the retrospective gating method. However, the most important disadvantage of prospective triggering lies in the fact that images can be reconstructed only for a preselected phase of the cardiac cycle and functional assessment of the heart is thus not feasible.

In comparison with CMR, cardiac CT has worse temporal resolution (75–250 ms) but better spatial resolution (0.5–1 mm) [8].

Cardiac CT is always associated with a certain radiation dose that usually varies from 1 to 15 mSv, depending on the scanning protocol. Iodinated contrast agents are used in most cardiac CT examinations.

Beta blockers and other drugs with negative chronotropic properties, such as ivabradine and verapamil, are administered in order to achieve a target heart rate, usually less than 65 beats per minute, minimizing motion artefacts.

3.2. Left Atrial Morphology. The LA represents a complex structure that consists of three compartments of different embryonic origin: the anterior LA (ALA), the venous LA (VLA), and the LA appendage (LAA).

The ALA forms the anterior and central parts of the LA. The LAA is a tubular structure that bulges out superiorly and in a leftward direction. The VLA receives blood from the pulmonary veins and represents the remaining part of the LA [62].

The average wall thickness of the LA varies between subjects in sinus rhythm and those with various types of atrial fibrillation (AF). In patients with paroxysmal AF, the LA wall measured by CT is thicker compared to patients with long-standing, persistent AF as well as individuals in sinus rhythm. This is reflective of the LA wall structural remodelling that occurs in paroxysmal AF prior to LA dilatation, which occurs as the AF becomes persistent [63].

The LAA has variable shapes and number of lobes. Four different shapes have been described: cactus, chicken wing (Figure 5), windsock, and cauliflower. The cactus shape is defined as a dominant central lobe with limited overall length and one or more secondary lobes; the chicken wing shape is defined as a main lobe that bends from the proximal middle part of the LAA; the windsock shape is characterized by one dominant lobe with several secondary, or even tertiary, lobes; and the cauliflower shape describes LAA morphology with limited overall length and complex internal structures [64]. The chicken wing shape seems to be the most common morphological subtype of the LAA according to a study by Di Biase et al. [65]. In the study, 932 patients with AF were investigated either by CT or CMR, and it was demonstrated that patients with chicken wing LAA morphology were less likely to have an embolic event even after adjusting for comorbidities and $CHADS_2$ score.

The risk of stroke or transient ischemic attack (TIA) due to paradoxical embolism is associated not only with atrial septal defect but also with the presence of a patent foramen ovale (PFO) which is found in approximately 25% of the general population mainly. Higher risk of stroke or TIA is also connected with interatrial septal aneurysm and with the relatively recently described atrial septal pouch. An atrial septal pouch is a lesion characterized by incomplete fusion of the septal components and thus might serve as a site for thrombus formation and subsequent embolization [66].

Figure 5: Contrast-enhanced CT image showing the most common subtype of left atrial appendage called chicken wing.

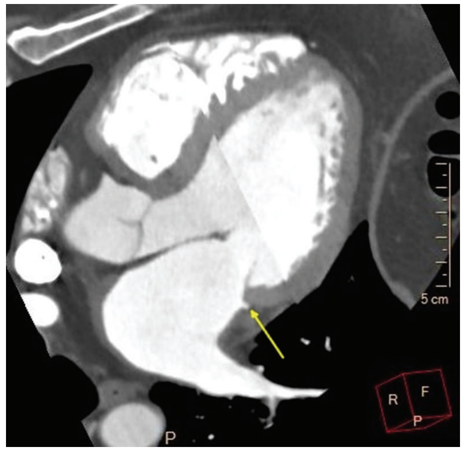


Figure 6: Contrast-enhanced CT image demonstrating a diverticulum (arrow) at the lateral part of the left atrium, close to the mitral valve.

Apart from abnormalities of the interatrial septum, the most common morphological variations of the LA are diverticula (Figure 6) and accessory appendages. Diverticula are defined as cyst-shaped protuberances that project outward from the heart cavity and are composed of a single muscular layer. The prevalence of diverticula ranges between 18% and 41% of subjects undergoing cardiac CT imaging, with a mean diverticular diameter of 4–6 mm [67]. The most common location of diverticula is the anterosuperior portion of the LA. The pathophysiology of their development is not clearly understood. It is hypothesized that they may be congenital, associated with incomplete development of accessory pulmonary veins or incomplete regression of cardinal veins, or they may be acquired, associated with ischemic heart disease or other heart pathologies. Diverticula are generally asymptomatic, although an association with thromboembolism and arrhythmias has been also reported [67].

Accessory LA appendages represent less common abnormalities with prevalence between 3 and 10% of subjects undergoing cardiac CT. LA accessory appendages are defined as sac-like structures with irregular contours that resemble the pectinate muscle and have narrower ostia than diverticula [68]. They are congenital and carry potential risk for thromboembolic events.

3.3. Left Atrial Size and Function. Left atrial size is associated with cardiovascular events and mortality [69, 70]. Cardiac magnetic resonance is considered to be the gold standard for assessment of LA size and function. Echocardiography still represents the most frequently used imaging tool for the quantification of LA size in daily clinical practice. However, with the advent of cardiac CT, information on LA morphology and size is readily available on every contrast-enhanced and even unenhanced scan of the heart. On the other hand, only CT scans acquired with retrospective gating provide information regarding LA function. Moreover, in scans obtained by prospective triggering, the LA size is assessable only in a predefined part of the cardiac cycle and so the true maximum size of the LA is usually not recorded.

In patients in sinus rhythm, there is clear evidence regarding the excellent correlation between LA size and function measured by CMR and CT. It is also well known that transthoracic echocardiography (TTE) tends to underestimate LA size and to overestimate LA systolic function in comparison with both CT and CMR [71–74].

Data regarding CT and CMR correlation in patients with ongoing AF have been sparse. Very recently Agner et al. conducted a study that included 34 patients with persistent AF, comparing TTE, CMR, and CT in the assessment of LA size expressed as LA maximal and minimal volumes (LAVmax and LAVmin, resp.) and LA systolic function represented by fractional area change (FC) [20]. Compared with CMR, CT overestimated both LA volumes (LAVmin by 8% and LAVmax by 10%). Echocardiographically derived LA volumes were underestimated in comparison with both CMR (LAVmin by 22% and LAVmax by 18%) and CT (LAVmin by 28% and LAVmax by 25%). Regarding LA systolic function, CT overestimated FC by 8%, and echocardiography overestimated FC by 23% in comparison with CMR. There was a close correlation between parameters obtained by CMR and CT. Moreover the intraobserver and interobserver agreements between these two methods were excellent. The correlation between TTE and CMR or CT was worse in all aspects of the assessment.

Recently, the advantage of unenhanced CT evaluation of the LA size was shown in a large cohort study. Mahabadi et al. reported the results of The Heinz Nixdorf Recall Study, which included 3958 subjects aged 45–75 years without coronary artery disease, stroke, atrial fibrillation, or flutter and without pacemaker or implanted defibrillator [75]. All subjects underwent non-contrast-enhanced CT scanning using the prospective triggering method. The area of the LA was measured, and major cardiovascular events during a mean follow-up of 8 years were evaluated. Endpoints were defined as coronary events, stroke, and cardiovascular death. Both LA size and its value indexed to BSA were strongly associated with the combined endpoint independently of traditional cardiovascular risk factors, even after adjusting for calcium score. The same relationship was also observed between LA size and each endpoint separately.

The LA represents a complex structure, with three compartments that are subject to differing degrees of involvement in AF patients. Park et al. conducted a study comprising 53 patients with paroxysmal AF, 43 individuals with persistent AF, and 48 control subjects in sinus rhythm who had no history of arterial hypertension, diabetes mellitus, ischemic heart disease, cardiomyopathy, or moderate to severe valvular disease. The authors assessed LA volumes indexed to body surface area (BSA) and ejection fraction of the entire LA as well as ejection fraction of each of its three components [62]. Not surprisingly, total LA volume was lowest in the control group and highest in the group of patients with persistent AF. In each of the three LA compartments, the maximum LA volume index was lowest in controls (LAA 4.8 mL/m^2; VLA 18.3 mL/m^2; ALA, 37.1 mL/m^2) and highest in patients with persistent AF (LAA 9.8 mL/m^2; VLA 30.0 mL/m^2; ALA 67.3 mL/m^2). The ejection fraction (EF) of the entire LA was highest in the control group and lowest in the group of patients with persistent AF (mean EF 42.89% versus 13.49%). Regarding the three LA compartments, the ejection fraction was highest in the LAA and lowest in the VLA in all three subgroups of patients.

According to this study and a report by Christiaens et al. [76], LAA parameters displayed relatively poor correlation with those of the LA, which can be explained by the fact that the LAA has a distinct pattern of contraction and a greater dependence on left ventricular function than on LA performance. The lowest regional systolic function was observed in the VLA, which may be explained by the fact that the VLA is a relatively immobile structure because the posterior LA wall is surrounded by the pericardium and parts of the great vessels of the heart. Moreover, poor contractility in the region of the pulmonary veins may contribute to the decline in VLA performance in patients with ongoing AF. It is also known that this region usually contains a high proportion of fibrosis in subjects after interventional or surgical isolation of pulmonary veins. The ALA is a mobile, smooth-walled structure, which is not fixed to the pericardium. It represents the largest compartment of the LA. Its systolic function is usually less compromised in comparison with VLA in subjects with AF and best reflects proper LA performance.

3.4. Left Atrial Thrombi. Thrombi are by far the most common form of LA mass and are found predominantly in the LAA. Well-known factors precipitating thrombus formation include structural and functional cardiac abnormalities, artificial cardiac implants, and hypercoagulable states [77].

Currently, TOE is considered to be the gold standard for detection of intra-atrial thrombi. The main advantages of TOE are related to its high temporal as well as spatial resolution, as well as the lack of radiation and nephrotoxic contrast agent exposure. However, TOE is a semi-invasive method, which needs to be performed with sedation in most patients and, even more importantly, is relatively highly operator-dependent.

Contrast-enhanced cardiac CT allows visualisation of the entire LA, including the LAA, and thus represents a diagnostic alternative to TOE for detection of intra-atrial thrombosis.

On CT, a thrombus appears as a homogeneous, low-attenuation lesion that classically does not enhance (Figure 7). However, an old thrombus may be organized, manifesting with a more heterogeneous appearance, with peripheral ring enhancement reflecting the formation of a fibrous capsule, or it may display high-attenuation areas corresponding to internal calcifications.

In various studies, different results in terms of sensitivity and specificity of intracardiac thrombus detection have been reported. Wu et al. performed a meta-analysis to explore the potential diagnostic value of CT in detecting LA or LAA thrombosis [78]. A total of 9 studies with 1646 patients were included in this meta-analysis. The mean CT sensitivity for identifying thrombus in the LA was 81% and the mean specificity 90%. The authors of this meta-analysis concluded that CT should be considered the best noninvasive alternative to TOE for detection of LA/LAA thrombosis.

The main issue in CT is to differentiate between true thrombi and a filling defect corresponding to circulatory stasis. Feuchtner et al. suggested four characteristic imaging features on cardiac CT that could be helpful in characterizing an incomplete filling defect of the LAA corresponding to stasis. The first of these features is the flow phenomenon, defined as the inhomogeneous appearance of mixed blood and contrast agent; the second feature is hypostatic layering, which is a sharp horizontal borderline between the contrast agent and nonmixed blood; the third feature is Hounsfield unit (HU) runoff, with decreasing density dorsally to ventrally; and the last feature is higher intralesional density in comparison with the density of thrombi (153.8±71 versus 71±46.6) [79]. In this study, a density threshold of 60.7 HU was able to differentiate a thrombus from an artefact with a diagnostic accuracy of 97%.

In order to improve the diagnostic accuracy of cardiac CT, Hur et al. suggested performing two-phase cardiac CT angiography [80]. Although this approach was associated with significant improvement in sensitivity and specificity (100% and 98%, resp.), it was also accompanied by higher radiation exposure due to the additional delayed enhanced scan. To avoid the higher radiation dose used with two-phase CT angiography while maintaining a high level of diagnostic accuracy, the same authors developed a new dual-enhanced single-phase CT angiography protocol [81]. This method is based on two injections of contrast agent, with a single scan performed in the late phase, 180 seconds after administration of the first contrast bolus. This study included 83 subjects, with an overall sensitivity and specificity of 96% and 100%, respectively, for the detection of thrombi and circulatory stasis in the LAA using CT.

Furthermore, quantitative analysis of the LAA/ascending aorta (AA) HU ratios was performed. The mean HU ratios significantly differed between thrombus and circulatory stasis (0.15 versus 0.27; $P = 0.001$). A cut-off value of 0.2 was most helpful in distinguishing between these two phenomena; a filling defect with a HU ratio below 0.2 is likely to be a

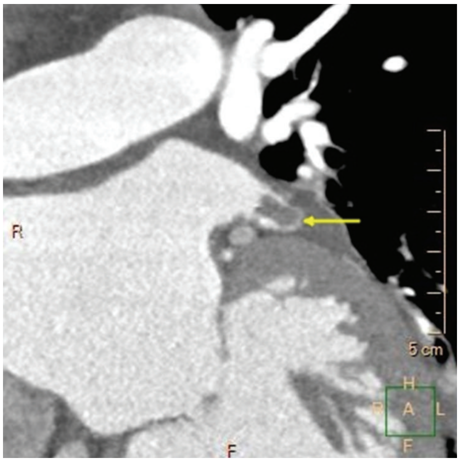


Figure 7: ECG-gated contrast-enhanced CT image depicting a thrombus in the left atrial appendage (arrow).

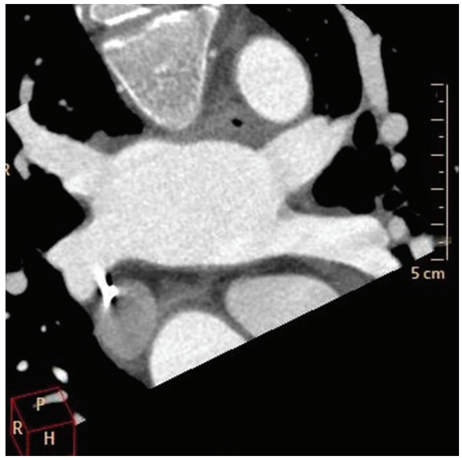


Figure 8: Contrast-enhanced CT scan showing two left-sided and two right-sided pulmonary veins.

thrombus. Two years later, the utility of quantitative analysis of the LAA/AA HU ratio was confirmed in a study of 101 consecutive patients with atrial fibrillation [82]. Moreover, this study showed that LAA/AA HU ratios were able to differentiate between grades of spontaneous echo contrast detected by TOE.

3.5. Left Atrium and Pulmonary Veins. With its ability to acquire a three-dimensional dataset accurately depicting LA and pulmonary venous anatomy, cardiac CT is currently the most commonly used imaging modality for pulmonary vein assessment in many centres, especially if interventional AF treatment is planned.

Approximately 70% of the general population has the classical configuration of four pulmonary veins: left superior and inferior pulmonary veins and right superior and inferior pulmonary veins, with four independent ostia (Figure 8) [83]. Pulmonary venous variations or abnormalities are related to the complex development of the venous system during first weeks of gestation. The most frequent abnormalities are left-sided pulmonary veins with a common ostium and a third right-sided pulmonary vein [84]. Pulmonary vein ostia have variable diameters, usually ranging between 9 and 13 mm in patients without AF [85] and between 12 and 24 mm in individuals with AF undergoing AF ablation procedure [86].

The clinical utility of CT imaging prior to AF ablation procedures includes preablation imaging of the LA and pulmonary veins to exclude intra-atrial thrombosis and to detect anatomical variants; depiction of the anatomical relationship between the LA, oesophagus, and adjacent vascular structures; creation of a 3D dataset of the LA and pulmonary veins for fusion with electroanatomical mapping data; assessment of morphological remodelling of the LA and pulmonary veins; and, finally, acquisition of a dataset useful for the detection of post-procedure complications (e.g., pulmonary vein stenosis) [35].

The presentation and clinical course of pulmonary vein stenosis vary widely from asymptomatic to highly symptomatic cases. Symptoms usually correlate with the number of the stenotic veins, the severity of the stenosis, the time course of the stenosis, compensatory mechanisms, and development of collaterals. The frequency of right superior, left superior, and left inferior pulmonary veins involvement is similar. The right inferior and right middle pulmonary veins are infrequently involved [87]. Minor stenoses that are defined as <50% luminal narrowing usually show no further progression and are associated with favorable outcome [88]. For detection and grading of the pulmonary vein stenosis severity after AF ablation procedure, the knowledge of the initial pulmonary vein diameters seems to be essential.

3.6. Left Atrial Tumours. Cardiac CT represents an alternative or complementary technique to echocardiography and CMR for the characterization of masses in the LA.

Myxomas are the most common primary cardiac tumours, predominantly localized in the LA. Typically, myxomas are solitary, pedunculated lesions attached to the interatrial septum (Figure 9). In unenhanced scans, myxomas have lower attenuation compared with surrounding blood, and their attenuation is usually heterogeneous. On contrast-enhanced scans, this tumour is usually a heterogeneously enhancing structure, with varying degrees of attenuation corresponding to areas of hemorrhage, necrosis, cyst formation, and calcification [77].

Secondary cardiac tumours are at least thirty times more common than primary tumours. Metastases to the heart are mostly associated with lung and breast tumours. Heart involvement is also frequently associated with the progression of various types of lymphomas. Features suggestive of a malignant mass in the LA are a filling defect with poorly defined margins, a lesion crossing tissue planes, an associated pericardial effusion, or the presence of an extracardiac tumour. Metastases are usually multiple and in most cases they involve pericardium and, less frequently, the

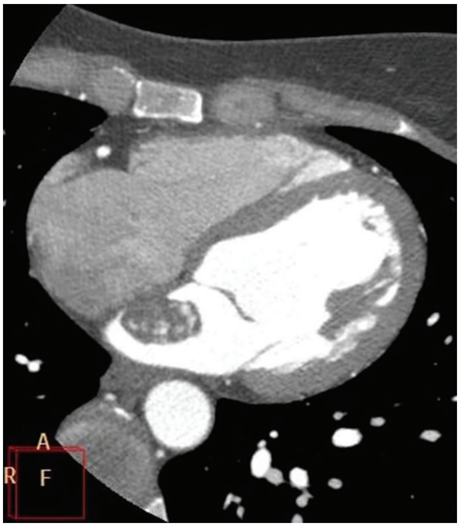


Figure 9: Contrast-enhanced CT image depicting left atrial myxoma attached to the interatrial septum.

myocardium or endocardium. Isolated LA involvement is uncommon in secondary tumours.

4. Conclusions

Both CMR and cardiac CT currently represent very important imaging modalities used for the comprehensive evaluation of the LA in various clinical settings. Cardiac magnetic resonance is considered to be the gold standard for volumetric assessment of left atrial size. Late gadolinium enhancement CMR offers unique information about the presence of LA scaring that may be used for optimizing the treatment of patients suffering from atrial arrhythmias. Cardiac CT is regarded as the method of choice for evaluation of pulmonary vein and LA anatomy before catheter ablation procedures for AF and also the most useful imaging modality for detection of pulmonary vein stenosis after RFA. Cardiac CT represents an alternative to TOE in exclusion of LA thrombosis. Cardiac magnetic resonance as well as CT also plays very important role in characterizing LA morphological variants and pathological intra-atrial masses.

Conflict of Interests

The authors declare that they do not have any conflict of interests.

Authors' Contribution

Petr Kuchynka and Jana Podzimkova contributed to this review equally.

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Review Article

Echocardiographic Evaluation of Left Atrial Mechanics: Function, History, Novel Techniques, Advantages, and Pitfalls

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Left atrial (LA) functional analysis has an established role in assessing left ventricular diastolic function. The current standard echocardiographic parameters used to study left ventricular diastolic function include pulsed-wave Doppler mitral inflow analysis, tissue Doppler imaging measurements, and LA dimension estimation. However, the above-mentioned parameters do not directly quantify LA performance. Deformation studies using strain and strain-rate imaging to assess LA function were validated in previous research, but this technique is not currently used in routine clinical practice. This review discusses the history, importance, and pitfalls of strain technology for the analysis of LA mechanics.

1. Introduction

The left atrium modulates left ventricular filling and cardiac performance through its roles as a reservoir [1–3], conduit [4], and booster pump [5]. Atrial myocardial deformation properties predict the maintenance of sinus rhythm after external cardioversion [6]. LA function was previously estimated using angiography [3], micromanometry [7, 8], and pulmonary pressure measurements [9, 10]. Doppler techniques [11–14] and strain technology [6, 15–17] are both new methods for the noninvasive evaluation of atrial mechanics [18]. Systemic hypertension patients with contractile function changes, left-sided end-diastolic pressure increases, and volume increases are predisposed to AF (AF). AF is the most common arrhythmia in humans and is characterized by disorganized atrial muscular activation with no effective atrial contraction. The atrial booster pump function is lost due to asynchronous atrial contractions during AF. This loss is associated with a fall in cardiac output, which has particular relevance in ventricular hypertrophy and ischemic heart disease, in which diastolic performance is already abnormal [19]. Standard evaluations of diastolic function using pulsed-wave (PW) Doppler of mitral inflow and tissue Doppler imaging (TDI) supplemented with LA deformation studies can diagnose early LA disease processes, thereby guiding treatments to prevent the development or recurrence of AF. Strain and strain-rate imaging to assess LA function in hypertensive patients with normal LA size demonstrated a lower reservoir function in each LA segment that was independent of age, sex, and heart rate [20].

Patients with diabetes and normal LA size have impaired LA deformation mechanics [21]. Additionally, the coexistence of both diseases impairs LA performance in an additive manner [21].

This paper explains the application of these novel techniques to assess LA function and critically discusses the pitfalls, problems, and impacts of these noninvasive imaging techniques. This review also explains how LA deformation assessments in routine clinical practice may facilitate appropriate AF management strategies and guide treatments to prevent AF.

2. History and Invasive Approaches of Atrial Function Assessment

William Harvey discussed the important role of the auricles in 1628: *"blood enters the ventricles... by the beat of the auricles"* and *"... they are filled as reservoirs"* [22]. A young American who studied the physiological properties of frog hearts in Leipzig in 1869 described the special "electric" nature of heart muscle [23]. Contrary to our scientific expectation, Howell and Donaldson but not Starling described the influence of fluid volume on ventricular performance for the first time in 1884. Frank [24] laid the foundation for the basic regulation of the Frank-Starling Law in 1895. Henderson, in 1906 [25], and Henderson and Barringer Jr., in 1913 [26], suggested fixed relaxation and diastolic capacity patterns. In 1911, Gesell [27] described the influence of auricular systole and its relationship to left ventricular output, and Patterson and Starling further described the impact of venous inflow for determining cardiac output and the role of the connections between venous inflow and outflow in the early 1900s [28]. Independently of Starling and coworkers, the German physiologist Straub [29] published the role of diastolic filling (venous pooling) on ventricular performance, and Wiggers [30] examined which factors influenced right ventricular function. Wiggers [31], who directly witnessed the interesting era from 1900 to 1950 subsequently described the determinants of cardiac performance in the 1950s. Braunwald and coworkers initiated research on the invasive measurements of atrial pressure combined with left ventricular pressures [32]. The relationship between increased left ventricular end-diastolic pressure (LVEDP) and elevated mean LA pressure in patients with left ventricular disease was described for the first time in 1961 [33]. The conduit function can be measured invasively [34] using volume/pressure curves. The experimental and hemodynamic era of heart examinations laid the groundwork for all future noninvasive investigations. Suga [4] concluded that atrial compliance was an important determinant of heart performance as a whole. The contractile nature of nature atria is not fully consistent with the present assumptions that atrial compliance is linear and constant [4]. The normal filling process of more than half of the ventricle during diastole before atrial contraction must be considered. Atrial contraction and deformation are consecutively affected in pathological situations in which the elastic properties of the myocardium are altered [35], leading to changes in the secretory function of the atria [36]. The hemodynamic role of the atria in regulating sodium and as a secretory organ dominated the literature in the late 1980s [36, 37]. The elastic properties of the myocardium and diastolic function have many determinants, which represent a broad area of research [7]. Ideally, simultaneously conducted chamber pressure, volume, flow, and neurohormonal factor (e.g., adrenalin, cortisol, and atrial natriuretic factor) measurements should be considered to examine the LV and LA elastic properties and systolic functions. In 1986, Ishida et al. [38] documented changes in transmitral flow, especially reduced early diastolic transmitral flow during increased afterload, using an invasive technique. Left ventricular filling dynamics and the influence of ventricular relaxation on LA pressure were examined in dogs and were compared to mitral flow. In 1988, Appleton et al. showed a significant relationship between pulmonary wedge pressures and transmitral Doppler velocities [11]. In 1991 [39] and 1997 [40], Thomas et al. compared LA pressures, left ventricular pressures, and transmitral Doppler flow or pulmonary venous flow (Figure 1). Ommen et al. [41] and the Mayo clinic working group simultaneously documented the clinical utility of Doppler and TDI in a comparative Doppler-catheterization study and demonstrated that the noninvasive assessment of LV filling pressures is an important clinical tool.

3. 2D/3D Echocardiography

Echocardiography provides a broad range of information on anatomic and functional changes to heart structures over time [42, 43]. Two-dimensional/three-dimensional (2D/3D) echocardiographic evaluation offers robust structural and functional information for the entire heart. Time-tested one-dimensional M-mode echocardiographic recordings can examine changes over the systolic and diastolic time periods during the cardiac cycle [44]. LA size is commonly estimated using M-mode-derived diameters. Reliable measurements can only be obtained using multiplane measurements [45, 46]. LA size is a strong predictor of clinical outcome in several conditions [47–49]. LA size has been proposed as a barometer of diastolic burden and an indicator of the magnitude and duration of diastolic disease [50]. The measurement of LA size in M-mode must be avoided due to the ovoid shape of the atrium. However, further evaluations of LA reservoir function and LA stiffness using 2D measurements have been validated [2]. 3D echocardiography was recently used to reliably measure LA sizes/volumes [51], and this method is the most robust solution for reliable LA size measurements [52, 53]. 3D echocardiography yields more reliable size/volume measurements but is more time consuming; furthermore, the differences in LA volume demonstrate only a minor, nonsignificant improvement [54]. The combined use of conventional 3D echocardiography and strain technology to assess LA size and function will likely play a more definitive role in the future [55, 56]. A central role for the assessment of atrial function using this technology is discussed further in this paper.

Using conventional 2D echocardiography, Saraiva et al. [16] obtained practicable measurements and normal values (Table 1(a)), and Todaro et al. [18] obtained complementary measurements (Table 1(b)).

4. PW-Doppler, PW-TDI, and Color TDI

Diastolic disease was already clinically recognized in the early 1980s [12, 57, 58] but was difficult to detect or quantify by all except well-educated cardiologists until 1982 [14]. Before the introduction of pulsed Doppler by Kitabatake et al. in 1982

Table 1: (a) Two-dimensional echocardiographic of LA volume and function in healthy volunteers ($n = 64$) Saraiva et al. [16]. Data are expressed as the means ± SD. (b) According to Todaro et al. [18].

(a)

Variable	Value
Maximum LA volume index (mL/m^2)	21.9 ± 5.1
Minimum LA volume index (mL/m^2)	7.3 ± 5.0
Precontraction LA volume index (mL/m^2)	12.1 ± 4.4
Total LA stroke volume (mL)	28.0 ± 7.7
Total LA emptying fraction (%)	70.3 ± 9.2
Active LA stroke volume (mL)	10.6 ± 5.0
Active LA emptying fraction (%)	46.6 ± 11.7
Passive LA stroke volume (mL)	17.5 ± 6.0
Passive LA emptying fraction (%)	44.3 ± 12.1
LA expansion index (%)	271.5 ± 126.4

Total LA stroke volume: maximum LA volume − minimum LA volume. Active LA stroke volume: precontraction LA volume − minimum LA volume. Passive LA stroke volume: maximum LA volume − precontraction LA volume. The total LA emptying fraction: (total LA stroke volume/maximum LA volume) × 100. The active LA emptying fraction: (active LA stroke volume/precontraction LA volume) × 100. The passive LA emptying fraction: (passive LA stroke volume/maximum LA volume) × 100. LA expansion index: (total LA stroke volume/minimum LA volume) × 100.

(b)

LA passive volumes
(i) Preatrial contraction volume (V_{preA}), measured at the onset of the P-wave using an electrocardiogram (ECG).
(ii) Minimal LA volume ($V_{\min}$), measured at the closure of the mitral valve and end-diastole.
(iii) Maximal LA volume ($V_{\max}$), measured just before the opening of the mitral valve in end-systole.
LA active volumes
(i) LA reservoir volume ($V_{\max} - V_{\min}$)
(ii) LA conduit volume (LV total stroke volume − LA reservoir volume)
(iii) LA passive emptying volume ($V_{\max} - V_{\text{preA}}$)
(iv) LA contractile volume ($V_{\text{preA}} - V_{\min}$)

[14], echocardiography using mitral leaflet motion analysis was used to demonstrate impaired early ventricular filling [59]. The assessment of diastolic heart failure using Doppler has become a fixed, integral part of European working group guidelines [60, 61]. PW-Doppler, which was validated using invasive measurements [11, 40, 41, 62], is the most widely used technique to directly analyze diastolic function and indirectly analyze atrial function [2, 11, 12, 14, 35, 63]. Mitral and pulmonary flow velocities reliably correlate to mean LA pressures and to pressure changes [39, 40, 62]. LA function has 3 phases: reservoir (inflow during ventricular systole), conduit (passive emptying during ventricular relaxation and diastasis), and contraction (active emptying near ventricular end-diastole) [2]. All of these properties are easily analyzed using PW-Doppler [64, 65]. Impaired diastolic function can be detected using a simple method and elementary echocardiography equipment [35, 66, 67]. The simplicity of this technique is its most important advantage (Figure 1) based on all known reservations today [68].

A lower peak early diastolic velocity ($V_{\max}$ E = passive inflow) and a comparatively higher atrial contraction velocity ($V_{\max}$ A = active inflow) are established signs of diastolic dysfunction [64, 66]. The combined use of Doppler measurements and 2D echocardiography was proposed to estimate the "atrial ejection force (AEF)" (Mass × Acceleration) [69]. In this case, the following formula was used:

$$\text{Atrial ejection force} = 0.5 \times p \times \text{Mitral orifice area} \times (\text{Peak A velocity})^2, \quad (1)$$

where p is the density of blood ($p = 1.06\,\text{g/cm}^3$) and the units of force are measured in g-cm/s^{-2} or dynes.

LV diastolic dysfunction measured using a simple Doppler technique is a strong predictor of first-diagnosed nonvalvular or incident AF [48, 70]. Diastolic disease is the leading cause of the atrial enlargement and LA pressure elevation associated with AF [65]. Sutherland et al. (1994) presented the first clinical use of color TDI [71], and Donovan et al. used this technique in healthy volunteers [72]. Sohn et al. [73] first described a "pseudonormalization" of diastolic function using Doppler indices (PW-TDI) by comparing transmitral PW-Doppler velocities to PW-TDI recordings on the septal side of the mitral annulus. Pseudonormalization was described as a normal pattern of transmitral flow (E > A) with reverse velocities derived by PW-TDI ($E' < A'$). Sohn et al. presented a connection to the suggestions of Sutherland et al. [71] based on suggestions of Alam and Hoglund [74] on examinations of diastolic atrioventricular plane displacement using M-mode echocardiography. Within the same year, Nagueh et al. [75] published similar observations using PW-TDI measurements from the septal and lateral sides of the mitral annulus. PW-TDI measurements of the lateral side of the mitral annulus showed higher velocities than those of the septal side. Park et al. suggested that the lateral E/Ea PW-TDI ratio may be more reflective of true LV diastolic function [76]. Similar observations were described by Kim et al. [77] using TDI. This working group suggested an overestimation of diastolic dysfunction using septal e'/a' and proposed a lateral TDI e'/a' ratio as an indicator of early but not of advanced diastolic dysfunction in subjects with a PW-Doppler mitral inflow ratio of E/A > 1 and a septal TDI ratio of $e'/a' < 1$.

The diastolic motion of the mitral annulus measured by PW-TDI was validated in animal experiments using invasive measurements [78]. Garcia et al. suggested new Doppler echocardiographic applications for evaluating diastolic function [79]. Color TDI was suggested for analyzing diastolic function, but the introduction of this technique into routine clinical use failed.

Poulsen suggested 4 grades of diastolic dysfunction in his doctoral thesis [12]. Based on Sohn et al. [73] and his own serial investigations [63, 80], Poulsen suggested 4 grades of diastolic dysfunction in his doctoral thesis [12].

Oh et al. [35] postulated 3 grades of diastolic dysfunction (Figure 2). These authors illustrated a schematic diagram of the "sucking" of blood into the left ventricle from the left

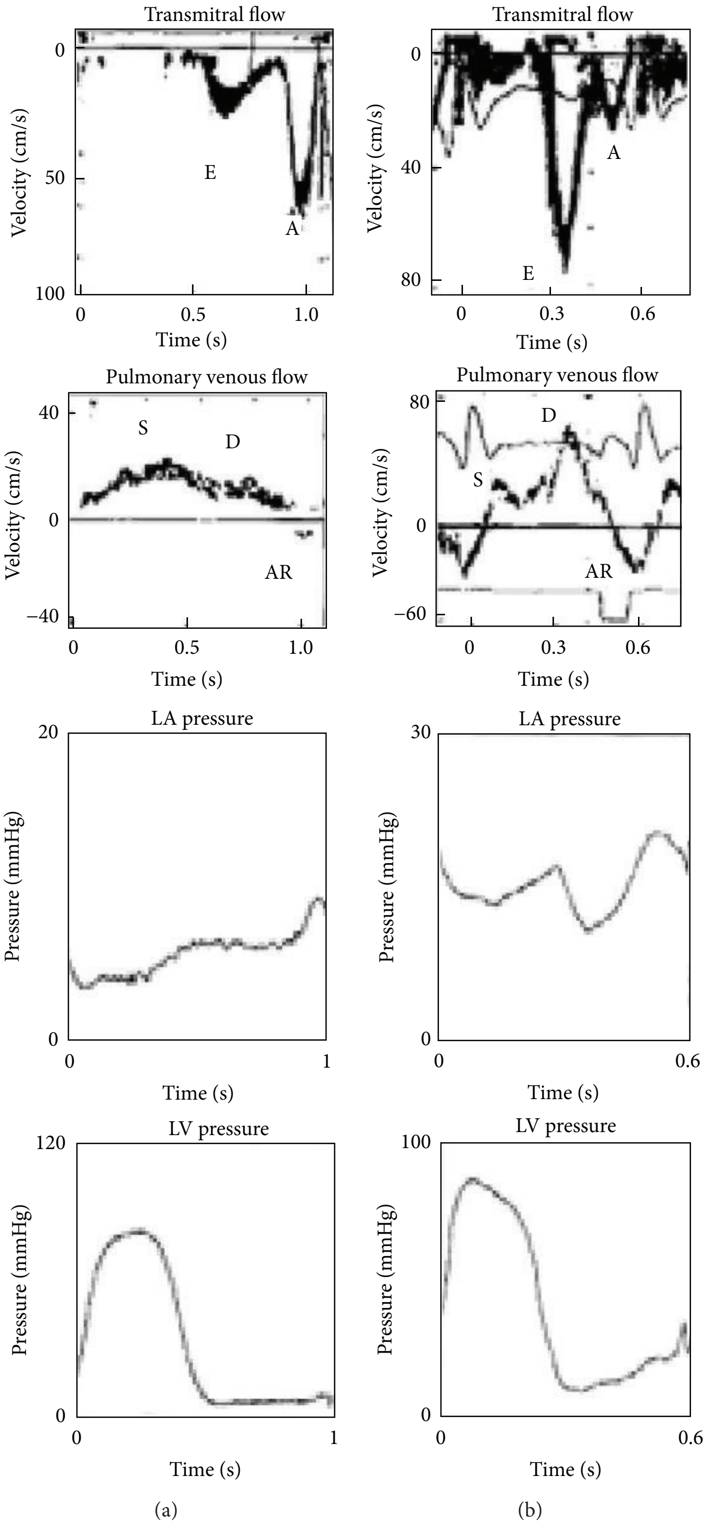


Figure 1: (a) Doppler and hemodynamic flow and pressure curves in patients with a delayed relaxation filling pattern. (b) Patients with restrictive filling patterns, adapted from Thomas et al. [40].

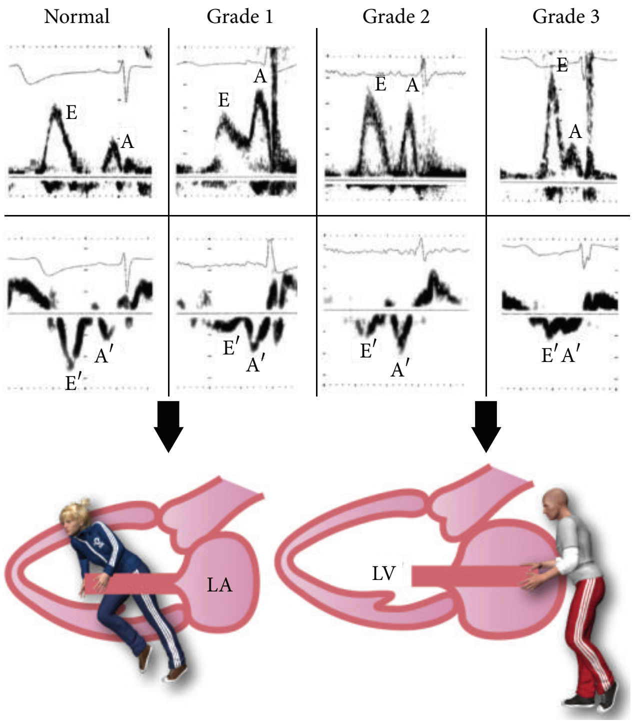
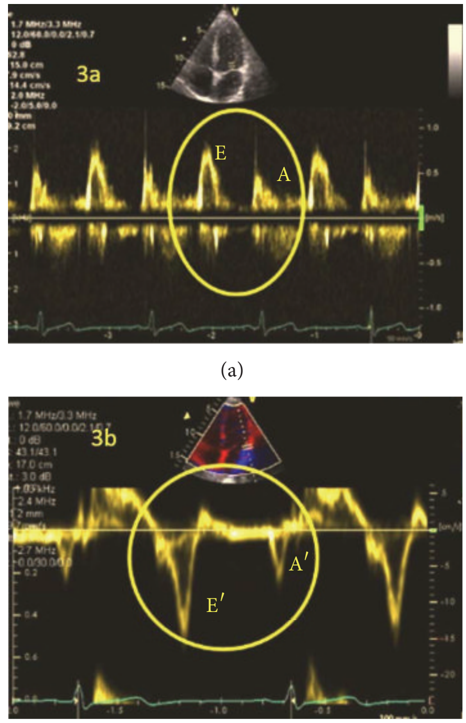


Figure 2: Grade one shows a reduced E/A ratio mitral inflow, measured by PW-Doppler, and a reduced E′/A′ ratio, measured by PW-TDI. Grade 2 represents "pseudonormalization," and Grade 3 represents restrictive physiology [35, 73].



(a)

(b)

Figure 3: Normal diastolic function in PW-Doppler (a) or TDI (b) on the lateral side of the mitral annulus.

atrium by good relaxation or the "pushing" of blood into the left ventricle by an increased filling pressure in patients with diastolic dysfunction.

Of all of the proposed parameters, only e′ (E′) and a′ (A′) derived from TDI (Figure 3(b)) (earlier from conventional PW-Doppler) [41] were validated and passed into routine clinical practice. The parameters were used with varying relevance [35, 68, 77] and in different combinations [68] and were associated with the pitfalls of angle dependency [71, 81], reproducibility, and invasive validation [68, 82] (Figure 3(b)). Hayashi et al. [81] demonstrated angle dependency and lower mitral annulus motion measurement values using TDI.

Kasner et al. [68] did not recommend the single use of PW-Doppler mitral inflow measurements and proposed the LV filling index E/E'_{lateral} as the best index to detect diastolic dysfunction in patients with heart failure and a normal ejection fraction (EF); Ommen et al. [41] suggested a similar index.

Mullens et al. [83] suggested that the E/E′ ratio (E/Ea ratio in their publication) is not reliable in patients with advanced systolic heart failure. Thus, the E/E′ ratio alone may not be reliable in predicting intracardiac filling pressures. The authors suggested a need to refine the broad clinical use of the mitral E/E′ ratio to estimate filling pressures and cautioned against the direct inference of relationships in patients with a decompensated state with significant LV systolic dysfunction, cardiac remodeling, or biventricular pacing.

Galderisi et al. [84] recommended using the lateral E/E′ ratio to predict a pulmonary capillary wedge pressure (PCWP) >18 mmHg in patients with coronary disease.

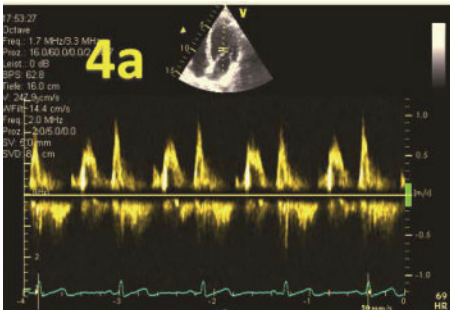
Bhella et al. [85] made a radical statement regarding echocardiographic indices derived from TDI ratios. The authors advised that the noninvasive indices E/E′ and E/Vp are not reliable for tracking changes in the left-sided filling pressure in healthy subjects or in patients with heart failure and preserved EF.

Despite the reliability of TDI [82], problems with the measurements include day-to-day variability [86] and inter- and intraobserver reproducibility [82, 86]. Additionally, dislocations from the mitral annulus to the lateral ventricular wall may produce different measurements (Figures 4(b) and 4(c)). According to statistical decision and information theory principles for decision making, using the recommended indices for decision making becomes problematic due to the many different opinions regarding TDI-derived parameters [87].

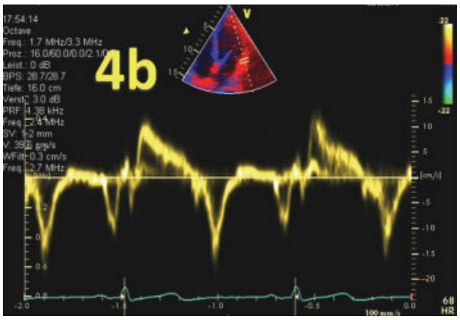
As a whole, the heart acts as a suction pump, but the atrium represents an important component of a functioning cardiovascular system [88]. The muscular architecture of the atrium [16, 89] and the left ventricular fibers [90] reveal the impact of deformation on atrial [16, 89, 91] and ventricular function [92–94]. TDI [95] and strain imaging [96] were initially used as a diagnostic tool to detect ischemia but were further used [15] to identify strong indicators of diastolic disease-associated diastolic dysfunction and atrial burden.

5. Strain

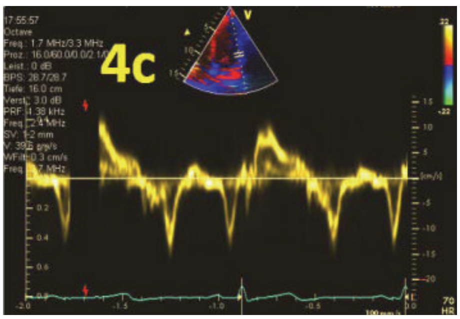
Di Salvo et al. [6] measured atrial wall velocities using sample volumes in patients with AF and reference subjects and



(a)



(b)



(c)

Figure 4: Pitfalls of the E/A and E/E′ ratio measured using PW-Doppler and TDI. Different values for diastolic dysfunction when measurements are performed using (a) PW-Doppler; (b) TDI measurement of lateral mitral valve annulus motion; (c) TDI measurement moved light to the lateral LV wall.

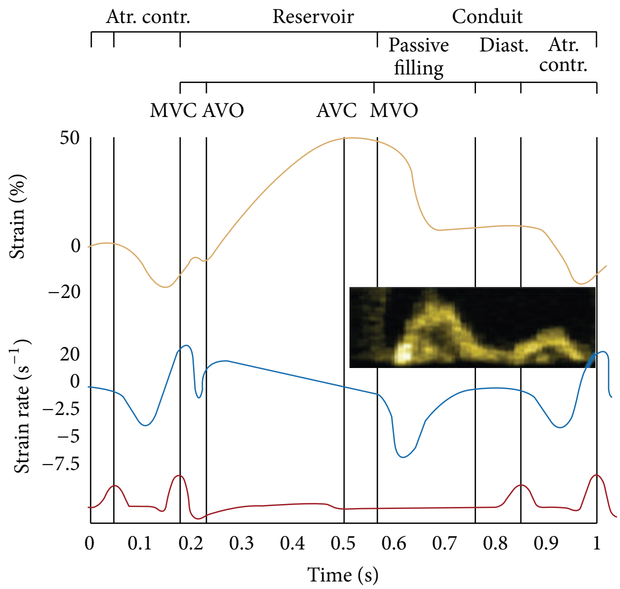


Figure 5: Atr. Contr: atrial contraction/contractile function of left atrium, MVC: mitral valve closure, AVO: aortic valve opening, AVC: aortic valve closure, MVO: mitral valve opening, and Diast.: diastasis.

calculated strain/strain rate values of the atrial walls. AF patients exhibited lower velocities using color TDI; however, interobserver values were not investigated in this study. Di Salvo et al. suggested peak systolic and peak early diastolic values of atrial velocity measured using TDI and peak systolic and peak early diastolic values measured using strain and strain rate, but only segmental values were examined. The estimated differences were significant between the two groups, but the differences were not sufficiently significant for use as a relevant specific diagnostic tool in the future. Based on a publication by Greenbaum et al. [90] and technical development, the deformation analysis ideas were introduced into the cardiology circuit [15, 94, 97].

Sutherland et al. first validated the clinical use of TDI to assess left ventricular function in 1994 [71]. His group (Sirbu et al.) subsequently demonstrated the value of LA strain imaging in assessing LA function [98]. This study first suggested using strain technology to analyze global atrial function and proposed 3 points on the strain (ε) curve as indicators of LA function: contractile function from 0.1 to 0.2 seconds, reservoir function from 0.3 to 0.5 seconds, and conduit function from 0.5 to 0.7 seconds (Figure 5).

The possibility for different estimations of "peak" values or time periods using strain (ε) or strain-rate curves exists during the time intervals of ECG intervals. Whether septal atrial wall or only "outside" mobile walls (lateral/posterior/anterior) should be considered remains unclear. Therefore, the possibility of introducing error exists using the segmental strain of the LA to estimate global strain values. Kokubu et al. [99] measured segmental atrial strain rate values in two-, three-, and four-chamber views by TDI in hypertensive patients after treatment with renin-angiotensin system (RAS) inhibitors. They proposed that strain rate imaging could detect LA dysfunction. A small significant difference was observed between hypertensive patients with and without dilated LA. An interobserver study was not performed, and the differences were not clinically useful.

Thomas et al. [100] proposed an atrial strain rate derived from a point on the midatrial septum as a marker for dysfunction; however, similarly to previous studies, this parameter did not initially merit much research or clinical impact. The idea of using and optimizing cardiac mechanics to assess LA function was eventually revisited in 2008 [101]. Schneider et al. suggested using mean strain and strain rate values measured during systole (LAs) and at early (LAe) and late (LAa) diastole as indicators of reverse atrial remodeling. Patients with higher atrial strain and strain rates after catheter ablation appeared to have a greater likelihood of maintaining sinus rhythm. The differences were small but significant and were derived from clinically useful values. However, a cut-off value could not be estimated. Cameli et al. [102] proposed global LA longitudinal strain values derived by speckle tracking of the left atrium, and peak atrial longitudinal strain (PALS) and time to peak longitudinal strain (TPLS) measurements were also proposed.

Kim et al. [91] proposed the use of global LA longitudinal strain during systole and early and late diastole, as well as of the related peak strain values. They showed no evidence of any systematic difference in the intra- or interobserver variability in 10 patients from their 54-subject study population. Vianna-Pinton et al. [103] demonstrated that the 2D speckle tracking technique was angle independent and was feasible in 94% of normal patients to assess regional differences in LA contractility using regional LA strain (LAε) and the regional LA strain rate (LAε'). The interobserver variability of global values was 5.7% for velocity and 6.5% for strain. A total of 13 LA regions, 5 regions adjoining the mitral annulus, and 5 regions in the midatrial wall were examined; in each view, the superior, or "roof," region, corresponding to the area encompassing the region between the 4 pulmonary veins, was also examined [103]. This paper described a specific time schedule of atrial contraction (early atrial activation of midseptal annulus and roof and later activation of the anterior and lateral annulus were suggested).

Saraiva et al. [16] suggested the use of LA strain measured using 2D speckle tracking as a new tool to evaluate LA function. They transcribed a similar methodology as the Sutherland working group: the ε positive peak, ε negative peak, and ε total (ε = strain (%)) were the suggested values. This working group suggested the following strain rate values: late negative peak strain rate ($SR_{\text{late neg peak}}$), positive peak strain rate ($SR_{\text{pos peak}}$), and early negative peak strain rate ($SR_{\text{early neg peak}}$). The global LA negative strain (LAε) and global LA SR late negative peak were not correlated with the active LA stroke volume or active LA emptying function [16].

Additionally, an assessment of the electromechanical delay (ca. 60 ms) between the interatrial septum and lateral wall was proposed [18].

Additional research groups [18, 104–106] suggested strain imaging as a novel echocardiographic technique to assess LA function. Cameli et al. [104] described systolic strain as peak atrial longitudinal strain (PALS) and atrial contraction as peak atrial contraction strain (PACS). Subsequently, 3D echocardiography was also suggested as a novel technique using strain analysis to assess LA function.

Speckle tracking was used to evaluate atrial function in different patient groups, including those with hypertension [20, 21, 107], diabetes [21, 107], systemic sclerosis [108], and hypertrophic cardiomyopathy [109], as well as in healthy athletes [109, 110]. Mondillo et al. [21] demonstrated impaired atrial strain values in hypertensive or diabetic patients. The coexistence of both conditions further impaired LA performance. Recently, Sahebjam et al. [20] demonstrated reduced strain and strain rate values in hypertensive patients compared with healthy controls.

Schneider et al. suggested that atrial strain and strain rate values of the atrial septum might predict sinus rhythm maintenance after AF ablation. In 2014, Spethmann et al. showed similar results in their study [111]. They suggested that LA mechanics might predict the success of pulmonary vein isolation in patients with AF. Peak positive strain (in this study, reservoir function = R_{LA}), early diastolic strain (conduit function = E_{LA}), and active atrial contraction (A_{LA}) were used in a pilot study prior to pulmonary vein ablation. The described parameters exhibited sufficient intraobserver variability (0.97 for R_{LA}, 0.92 for E_{LA}, and 0.99 for A_{LA}).

Severe mitral regurgitation is associated with LA dysfunction related to the presence of indications for mitral surgery. LA dysfunction measured using reservoir strain may be a valuable clinical marker for follow-up and decision making in conventional mitral surgery [112]. The reservoir function (strain, in %) and active emptying fraction (%) were significantly reduced (19 ± 7.7 versus 31 ± 6.1 and 24 ± 10 versus 32 ± 12, $P = 0.001$) in patients with mitral regurgitation and indications for mitral surgery compared with controls [112].

Diminished augmentation of the LA reservoir and passive emptying functions during dobutamine stress were strongly associated with cardiovascular events [113]. Assessment of the LA functional reserve may result in further improvements in prognostic risk stratification in patients with dilated cardiomyopathy (DCM) [113].

Hammerstingl et al. described reduced global longitudinal atrial strain as a predictor of AF recurrence [114]. In a 4-chamber view, global LA strain was significantly reduced in patients with recurrent AF compared with sinus rhythm maintenance (5.1 ± 6.7 versus 22.9 ± 11.7, $P = 0.0005$).

6. Conclusions

Strain imaging [115] is the most promising technology for the direct evaluation of LA function [116]. This imaging technique offers many opportunities to measure several quantitative parameters but unfortunately lacks clear standards and validation (Figure 6). Strain imaging begins with the establishment of the onset of time-point markers for analysis (QRS, atrial wave, or aortic closure) and ends with standardized online/offline atrial analyzing software tools from different vendors, which are lacking.

All current software options were designed to conduct left ventricle analyses; less software is available for atrial strain analyses. There is also a lack of standards or official consensus documents. The underlying problems are the theoretical presence of three segments, at a minimum, which can be placed in different positions and extensions or the analysis of six segments in different echo views (Figure 7). Different extensions and different time points lead to different values.

The four-chamber view (the most commonly used) provides atrial septal movement, which may influence the analyses as a whole in an unclear manner. Other issues include the relatively small "cut-off" values or overlapping areas for differential diagnoses or disease stages [87]. We have not progressed much further regarding establishing standards and reducing pitfalls between the first inception of strain imaging for the analysis of LA function [98] and the latest review [116]. The old parameters (Tables 1(a) and 1(b)) are valid, and the LA EF has a similar potential as strain to identify recurrent AF [114]. Doppler parameters

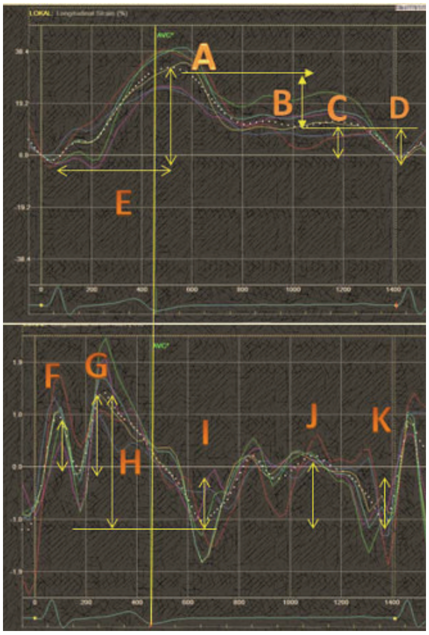


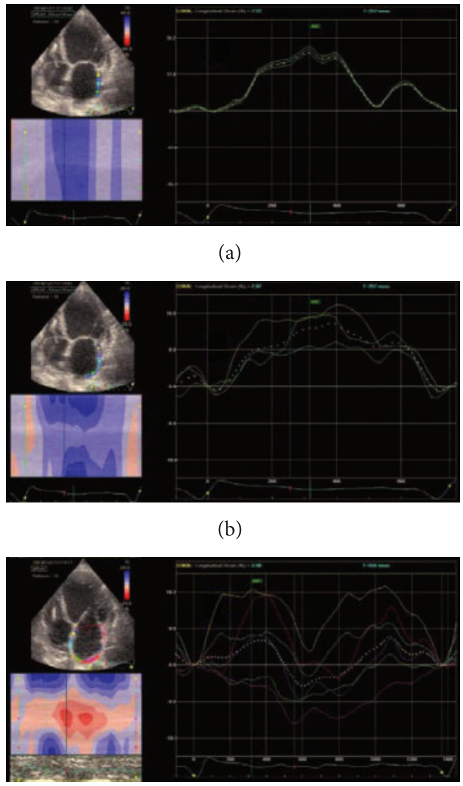
Figure 6: Suggested strain values; A: peak systolic strain (reservoir function), B: peak early diastolic strain (conduit function), C: peak late diastolic strain, D: peak negative diastolic strain, E: time to peak systolic strain, F: early peak systolic strain rate, G: late peak systolic strain rate, H: total systolic strain rate, I: peak negative early diastolic strain rate, and J: peak positive late diastolic strain rate.

such as the E/A ratio are valuable and easily obtained, and, most importantly, these parameters have stood the test of time. Global LA strain in the four-chamber view likely offers three interesting parameters in the absence of segmental failures of deformation: maximum positive strain (reservoir Figure 6(A)), late atrial positive strain (Figure 6(C)), and peak negative diastolic strain (Figure 6(D)). These two LA strain imaging parameters (Figures 6(A) and 6(B)) seem to have the most evidence [104] to support their clinical role. All strain parameters (Figure 6) required further standardization and additional comprehensive studies.

The development of a standardized software tool for the specific analysis of LA function and consequent experimental studies using the standardized parameters (either global or segmental) are needed. The measurement onset and time points must be standardized (onset QRS, P-wave, and aortic closure). Evaluations of intra- and interobserver variability according to the ventricular strain are required for all parameters [117]. The atrial wall is thinner, with less muscular mass; therefore, deformation measurements might display more variability on different ultrasound systems. Systematic studies are required in this field to develop clear, clinically valuable standards.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.



(a)

(b)

(c)

Figure 7: (a) Three-segment small extension (only the lateral wall), (b) three-segment larger extension (lateral and posterior walls), and (c) all six segments; different time points give different values.

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Review Article

Left Atrial Appendage: Physiology, Pathology, and Role as a Therapeutic Target

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Atrial fibrillation (AF) is the most common clinically relevant cardiac arrhythmia. AF poses patients at increased risk of thromboembolism, in particular ischemic stroke. The CHADS2 and CHA2DS2-VASc scores are useful in the assessment of thromboembolic risk in nonvalvular AF and are utilized in decision-making about treatment with oral anticoagulation (OAC). However, OAC is underutilized due to poor patient compliance and contraindications, especially major bleedings. The Virchow triad synthesizes the pathogenesis of thrombogenesis in AF: endocardial dysfunction, abnormal blood stasis, and altered hemostasis. This is especially prominent in the left atrial appendage (LAA), where the low flow reaches its minimum. The LAA is the remnant of the embryonic left atrium, with a complex and variable morphology predisposing to stasis, especially during AF. In patients with nonvalvular AF, 90% of thrombi are located in the LAA. So, left atrial appendage occlusion could be an interesting and effective procedure in thromboembolism prevention in AF. After exclusion of LAA as an embolic source, the remaining risk of thromboembolism does not longer justify the use of oral anticoagulants. Various surgical and catheter-based methods have been developed to exclude the LAA. This paper reviews the physiological and pathophysiological role of the LAA and catheter-based methods of LAA exclusion.

1. Introduction

The Left atrial appendage (LAA) has a complex anatomical structure that is distinct from the rest of the left atrium as it has different embryologic, anatomic, and pathophysiologic characteristics.

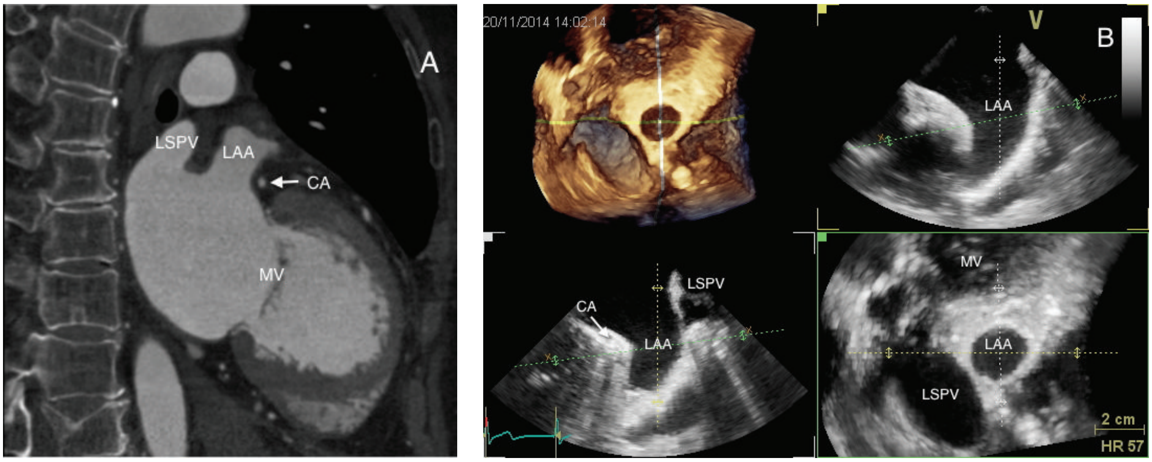
LAA is a remnant of the embryonic left atrium [1], while the rest of the left atrial cavity derives from an outgrowth of the pulmonary veins.

In order to define LAA anatomy and topographic relationships, multidetector computerized tomography (CT), and its high definition and transesophageal echocardiogram (TEE), in particular with the development of three-dimensional reconstructions, are the most accurate noninvasive imaging modalities. Cardiac magnetic resonance imaging (MRI) is an emerging technique in order to detect thrombi as well as LAA sizing [2], but its use in the clinical setting remains limited mainly due to its high costs and poor temporal resolution.

LAA is not just an embryologic remnant, but it seems to play an important role in the regulation of heart rate and fluid balance [3].

On the other hand, LAA has a key role in the thromboembolic risk [4] associated with atrial fibrillation (AF) and it could also have a possible triggering effect of atrial tachyarrhythmias [5].

Because of this role in physiology and pathophysiology, LAA is recently gaining attention as a therapeutic target especially in thromboembolism prevention in patients with AF.



(a) (b)

Figure 1: Left appendage anatomical relationship, as seen with cardiac CT scan (a) and 3D transesophageal echocardiography (b). LAA: left atrial appendage; LSPV: left superior pulmonary vein; CA: circumflex artery; MV: mitral valve.

In fact, it is the most common source of cardioembolic stroke in AF as LAA thrombus is present in up to 15% of patients in AF [6] and 90% of thrombus formation in nonvalvular AF is in LAA [7].

For this reason it has been defined as the "most lethal human appendage" [8] causing significant mortality and morbidity in AF patients.

CHADS2 score (cardiac failure, hypertension, age, diabetes, diabetes, and stroke) and the more recent CHA2DS2-VASc score (with the addition of gender, vascular disease) are useful tools to stratify thromboembolic risk in AF patients, guiding the decision for anticoagulation therapy [9, 10]. In fact, oral anticoagulation (OAC) has been shown to significantly reduce the risk of thromboembolism in numerous studies [11].

However, due to poor patient compliance, contraindications, and potential bleeding complications, OAC is underutilized in AF [12].

So, in certain clinical scenarios, when anticoagulation is contraindicated or has a high risk, LAA percutaneous closure is a safe and effective measure to prevent thromboembolism.

Considering that only 10% of the clinically relevant emboli in nonvalvular AF do not originate in the LAA [13], with the exclusion of LAA as an embolic source, the remaining small risk does not require any longer OAC with its inherent risk for side effects, especially major bleedings. Numerous methods have been developed to exclude the LAA, surgically or percutaneously, LAA [14, 15].

2. Physiology and Pathophysiology of the LAA

2.1. Anatomy and Physiology. The LAA is a remnant of the embryonic left atrium [1], lying in the left atrioventricular groove and in close relation with the left circumflex artery, with the left superior pulmonary vein posteriorly, with the mitral valve annulus medially, and with the left phrenic nerve laterally (Figure 1).

Anatomical studies have described numerous shapes of the LAA: as a long, narrow, tubular, and hooked structure [17].

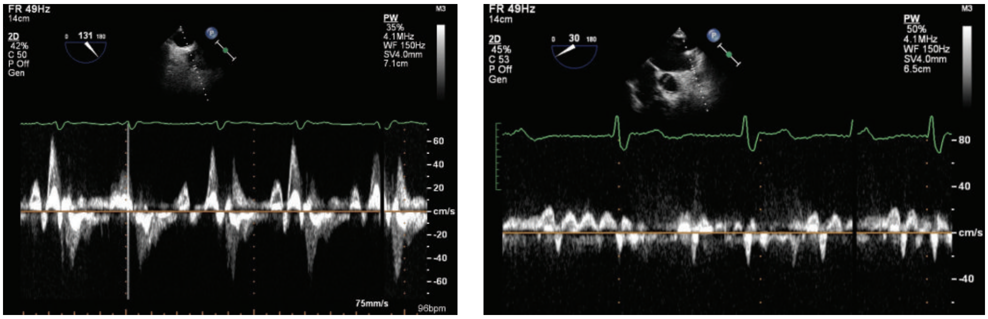
The shape of the LAA ostium is typically elliptical (68.9%), with a long diameter ranging from 10 to 40 mm and a maximal depth ranging from 16 to 51 mm [18]. A round shape is present only in 5.7% of cases. Interestingly, ostium diameters showed minimal changes during different phases of the cardiac cycle in sinus rhythm (maximal change 1 to 2 mm), while no change was observed during AF [19].

Veinot et al. [20] have examined 500 anatomical findings: in more than two-thirds of cases, LAA is composed of two or more lobes, located in different planes. Classically, the lobes head toward the atrioventricular groove and the basal surface of the left ventricle. This has to be kept in mind during imaging studies in order to rule out intracavitary thrombus: failure to view all the lobes or incomplete visualization of a lobe may account for underdiagnosis of LAA thrombosis.

Recently, a CT based study classified LAA morphology on the basis of the presence of a bend, giving to the LAA an appearance similar to a chicken wing (48% of cases). Others possible morphologies are cactus shape (30%), with a dominant central lobe and secondary lobes extending from the central lobe in both superior and inferior directions; windsock shape (19%), with 1 dominant lobe; cauliflower shape (3%), with limited overall length and complex internal characteristics [21].

Histologically, the LAA has a single layer of endothelium and contains pectinate muscles with variable thickness [19]. The anterolateral wall, close to the mitral valve, has the minimum thickness (0.5 mm): particular care should be taken to avoid perforation during invasive procedures.

As said before, the LAA does not seem to be just an embryologic remnant, a useless appendage. The LAA is responsible for several functions: it acts as a reservoir during left ventricular systole, a conduit for blood transiting from the pulmonary veins to the left ventricle during early diastole,



(a) (b)

Figure 2: Left atrial appendage emptying velocity during normal sinus rhythm (a) and during atrial fibrillation (b).

an active contractile chamber that augments left ventricular filling in late diastole, and a suction source that refills itself in early systole [22]. In fact, the LAA seems more distensible than the rest of the atrium and it could act as a volume reserve. Experimental findings during cardiac surgery demonstrated how LAA temporary exclusion augments LA pressure [23]. It is also possible that the LAA could contribute to stroke volume, due to its intrinsic contractile capability [24].

The LAA also has an endocrine role: it contains stretch-sensitive receptors that are able to influence heart rate and natriuretic peptides secretion in response to change in atrial pressure. A quantitative analysis of atrial natriuretic peptides (ANP) in excised LAAs revealed a content of approximately 30% of all cardiac ANP [25]. Experimental infusion of fluid in the LAA results in diuresis and natriuresis and increased heart rate, supporting a significant role of the LAA in regulating normal cardiac physiology [26].

However, little is known about these functions in a pathological LAA, as seen during AF or after LAA closure.

The LAA has a distinct pattern of contraction, extensively studied with TEE [27]. It has an augmented contractility in respect to the atrium; typically, it has a biphasic pattern of emptying, a first passive phase in protodiastole and a second active phase during left atrial contraction and a prominent monophasic pattern of filling (Figure 2(a)). During atrial fibrillation, the pattern is characterized by a rapid alternation of emptying and filling, with lower velocities (Figure 2(b)).

Abnormalities of the LAA function observed at TEE in AF (perturbations of LAA emptying peak flow velocity, LAA fractional area change and LAA velocities <0.2 m/sec), are associated with the occurrence of spontaneous echo-contrast and thrombus formation resulting from blood stagnation in the LA. These findings have been shown to be associated with the occurrence of ischemic strokes in several clinical reports [28].

2.2. Role of the LAA in Cardiac Pathophysiology. As mentioned before, the LAA is the most common source of cardioembolic stroke in nonvalvular AF (up to 90% of cases) [7].

The reasons why this happens are multiple, summed up by the Virchow triad [29]. First of all, the risk of thrombus formation depends on the hemodynamic function of the LAA. Three LAA flow patterns have been described:

(1) type I, characterized by a regular biphasic emptying pattern, occurring in sinus rhythm;

(2) type II, characterized by a saw-tooth emptying pattern, occurring in some patients with atrial fibrillation;

(3) type III, without any active emptying pattern, typically occurring during AF. This is associated with the highest incidence of spontaneous echo-contrast and thrombus [30].

A reduced LAA peak flow velocity is considered as one of the strongest independent predictors of an increased thromboembolic risk [31].

Furthermore a prothrombotic and hypercoagulable state in AF has been demonstrated, manifested by increased blood levels of markers, reflecting coagulation activity (e.g., prothrombin fragments 1 and 2, fibrinopeptide A, thrombin–antithrombin complexes, and D dimer) [32].

Eventually, atrial fibrillation leads to damages, fibrosis, and inflammation of the endothelium of the left atrium, especially of the LAA [33].

In addition to these factors, LAA shape and size have also been recently evaluated as additive risk factors: in fact spontaneous echo-contrast is most likely found in larger LAA with more complex anatomies [21].

3. LAA as a Target for Thromboembolic Risk Prevention

Although antiarrhythmic drugs and catheter ablation are effective in symptomatic relief for patients with atrial fibrillation, the prevention of thromboembolic events is still entrusted to oral anticoagulation (vitamin K antagonists, VKA), irrespective of the rhythm management strategy.

With the recent emergence of new antithrombotic drugs (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban), it became clear that VKA, although being more effective than aspirin and combination aspirin-clopidogrel, is often not well tolerated by patients, has a very narrow therapeutic range, and has a high risk for bleeding complications. However,

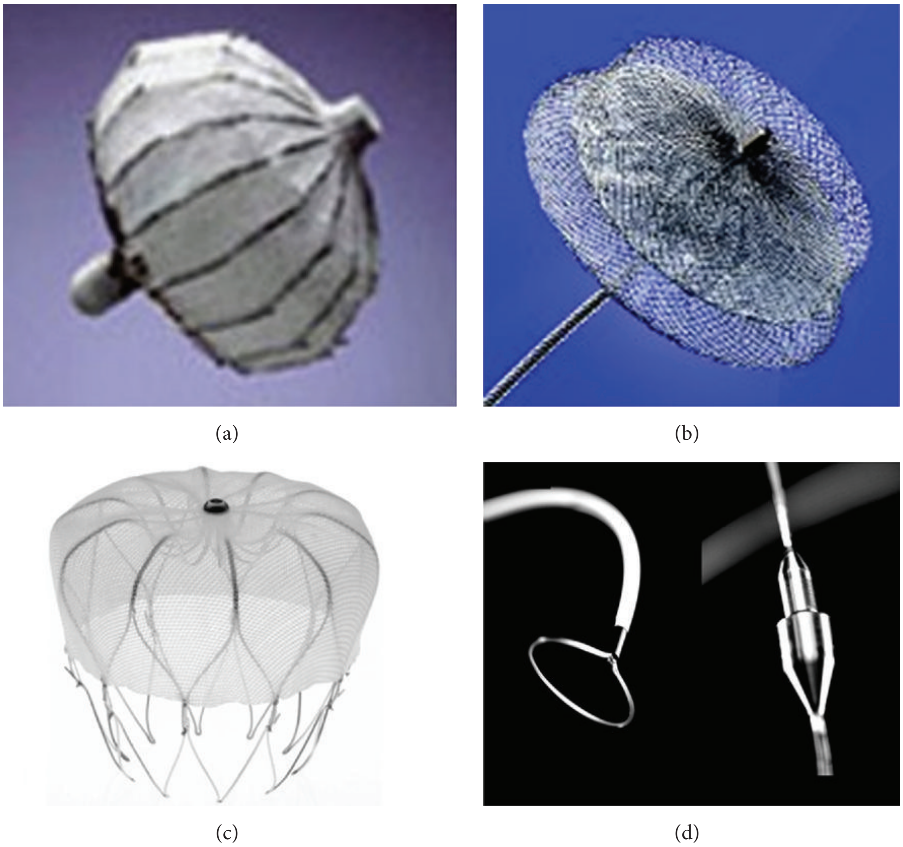


Figure 3: Left atrial appendage occlusion devices: PLAATO device, no longer available (a), Amplatzer Cardiac Plug (b), Watchman (c), and Lariat device (d).

the drugs mentioned above do not completely solve the risk of bleeding related to antithrombotic therapy.

This is why, over the years, several clinical trials have assessed the feasibility and efficacy of LAA occlusion as a tool for thromboembolism prevention in AF. The first interventions were performed by surgical ligation or removal of the LAA during valvular operations. In fact, LAA obliteration was first suggested as an addition to mitral valvotomy, even before the advent of cardiopulmonary bypass [4]. About fifty years later, interest in surgical LAA exclusion increased after the development of Maze procedure, performed by Cox, that was a reliable solution for the treatment of AF and included atrial appendage removal [34]. Since then, the procedure has evolved in two directions: LAA exclusion with sutures on the epicardial or endocardial surface and LAA excision through staples or removal and oversew. The surgical literature on LAA closure consists primarily of retrospective case series and, regardless of the approach used, showed that incomplete LAA closure may be worse than no closure [35]. All available studies show a failure rate between 10% [36] and 55% [37] with the consequent effect of potentially increasing the incidence of stroke.

The vast majority of patients, however, suffers from nonvalvular atrial fibrillation and has no indications for cardiac surgery: this is why in the last decade percutaneous approaches for LAA occlusion were developed. Obstruction of the LAA orifice with an occlusion device [38] or percutaneous suture ligation using an endocardial/epicardial approach [39] is the two alternatives (Figure 3).

The first percutaneous LAA occlusion was performed by the electrophysiologist Michael Lesh with a device called PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occluder) on 30 August 2001 [40].

After that, several studies using the PLAATO device have been published: in the international multicenter feasibility trials [41], device implantation was successful in 108 of 111 patients (97.3%) with only one cardiac tamponade and one major vascular complication. The postprocedural stroke incidence was lower than that projected by the clinical scores (mean CHADS2 score 2.5). In fact, the incidence of the major and minor stroke was under 2% during a mean follow-up period of about one year.

Further studies showed that the PLAATO device appeared to be effective in reducing the stroke risk in patients with AF (stroke incidence 2.3%/year versus 6.6%/year as predicted by CHADS2 score), with a small risk of major periprocedural events (procedural success 90%, cardiac tamponade 3.3%, acute mortality 1.1%, and device embolization 0.6%) [42].

However, the PLAATO device has been discontinued for commercial reasons and then it was withdrawn from the market.

The Amplatzer Cardiac Plug (ACP) has the longest clinical follow-up among the currently available LAA occluders [43].

Trials have shown that complications, such as pericardial effusion leading to cardiac tamponade, occurred in 2% of patients, as did the neurological events (Table 1).

Technical success was 97% and a relevant thrombus on the device during follow-up TEE was seen in 3%. The percentage of residual peridevice flow is very low: at 6 months, TEE is about 1%, probably due to the device's peculiar shape, with a disk that occludes the so-called "mouth" of the LAA. Generally, antithrombotic therapy after ACPs implant relies on double antiplatelet therapy instead of OAC.

The second generation of Amplatzer device, the so-called Amulet device, has recently been introduced in the market: Amulet data are available in only a few patients, although it was used in over 250 patients in Europe. The device [44, 45] has new features as compared to the first generation ACP as it shows good deliverability (96%–100% of procedural success) with 0%–5% pericardial effusion incidence and without acute strokes or device embolization.

The Watchman device is the only one evaluated in prospective, controlled, randomized trials (Table 2) examining its efficacy and safety (PROTECT AF trial [38] and PREVAIL trial [46]).

In the PROTECT AF, that enrolled 707 patients for 1065 patient-years of follow-up, a relative risk reduction of 46% of ischemic strokes and systemic thromboembolism (from 2.85 to 1.53) was observed in comparison to the control group, although a higher rate of adverse safety events was noted, mainly due to periprocedural complications such as pericardial effusion and procedural stroke typically related to air embolism.

Also the PREVAIL study, in patients with higher risk, demonstrated low-early and long-term primary and safety event rates.

Furthermore, a cost-efficacy analysis was carried out and showed that LAA occlusion was cost-effective when compared to warfarin and dabigatran (but only marginally with the latter drug) [47].

A subanalysis of patients enrolled in PROTECT AF showed that residual peridevice flow is possible after device implantation. However, small peridevice residual flow does not seem to have an impact on safety and clinical efficacy of Watchman implantation [48].

The WaveCrest device has recently received a CE mark as well, and it seems to provide a more superficial deployment with little or no manipulation within the LAA body. The WaveCrest device consists of a nitinol structure without exposed metal hub and with a foam layer facing the LAA to promote rapid organization and a PTFE layer facing the LA to reduce thrombus formation. Procedural and follow-up data are not available yet for this device.

The Lariat combined endocardial/epicardial suture ligation of the LAA uses a combination of transseptal placement of a temporary balloon in the LAA, magnet-tipped guidewires inserted into the LAA and the pericardial space, and a closure snare device. This device demonstrated successful LAA closure in a canine model [49]. Studies in the human population [50, 51] in almost 200 patients showed a good procedural success (93-94%). Early major complications were higher as compared to fully percutaneous devices: the incidence of pericardial effusion requiring pericardiocentesis was between 11% and 20%, and the incidence of major bleeding was 9% while another 9% of patients suffered LAA perforation needing open chest surgery. At the follow-up incidence of stroke, myocardial infarction was under 3%/year. Furthermore, LAA exclusion with this device appears to reduce AF burden [52], thus confirming the role of the LAA in triggering AF.

4. Imaging for Left Atrial Appendage Occlusion

Adequate imaging modalities are essential for successful LAA occlusion, by guiding preprocedural planning and periprocedural assessment and follow-up.

This usually requires TEE or CT. TEE is crucial in guiding the procedure of LAA occlusions [53], and it is recognized as the gold standard for it.

4.1. Preprocedural Assessment. At first, it is important to confirm the absence of thrombi in LAA before the procedure, in order to avoid a possible embolization with sheath or device manipulation.

The imaging technique that is more validated and more often used for this purpose is TEE: in some patients, there may still be difficulties in differentiating prominent pectinate muscles from LAA thrombi. However, the incidence of LAA thrombus (Figure 4(a)) or sludge (Figure 5) among patients undergoing AF ablation who have been adequately anticoagulated was found to be very low, and it is well correlated with the CHA2DS2-VASc score [54].

Dual-enhanced cardiac CT [55] and cardiac MRI [56] could also be useful for this purpose (Figure 4(b)).

Spontaneous echocardiographic contrast is diagnosed in the presence of smoke-like echoes with a characteristic swirling motion, when the gain settings have been increased in a stepwise manner.

A thrombus is diagnosed if an echo reflecting mass is evident in more than one imaging plane, with independent mobility.

If a thrombus is detected inside the LAA, it is prudent to optimize anticoagulation and reassess LAA status after 4 weeks of optimal anticoagulation therapy.

In case of persistence, it is possible to surgically remove the thrombus and exclude the LAA. Percutaneous procedures have also been performed in this setting with an embolic protection device in the supra-aortic trunks [57].

However, it seems prudent not to perform this procedure in case of LAA thrombosis.

Preprocedural TEE guides the decision of the device size: multiplane views (midesophageal 0°, 45°, 90°, and 135°) characterize LAA shape and morphology, facilitated by 3-dimensional reconstructions (Figure 6(a)).

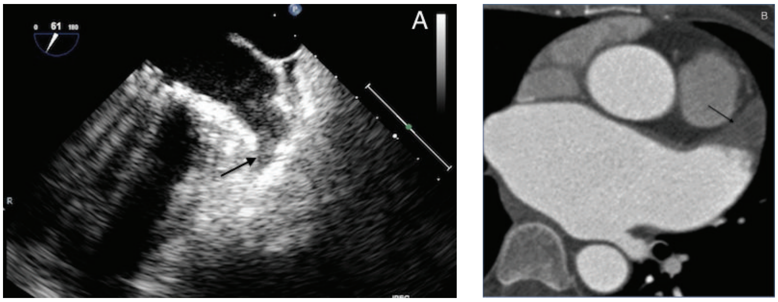
Table 1: Results with the Watchman device from Meier et al. [16].

Trial	Patients	Patients device/control	Comments	Average CHADS2 Score	Average CHA2DS2-VASc Score	Medical therapy	Efficacy events	Safety events	Successful implantation	Mean follow-up (months)	No warfarin	Primary efficacy event rate (per 100 patient-years)	Safety event rate
Pilot study	66	66/0	Nonrandomized cohort of patients undergoing Watchman implantation	1.8 ± 1.1		Warfarin plus ASA for 45 days and ASA for life	Death, stroke, systemic embolism, and major bleeding		88%	73 ± 25	91%	Actual stroke rate of 0.5%	4-device embolization
PROTECT AF	707	463/244 warfarin	Randomized noninferiority trial	2.2 ± 1.2	3.4	Warfarin plus ASA for 45 days, DAPT for 6 months, and ASA for life	Composite endpoint of stroke, cardiovascular death, and systemic embolism	Device embolization, major bleeding events, and pericardial effusion	88%	18 ± 10 43.4 ± 21.7	94%		
CAP registry	460	460/0	Nonrandomized registry of patients undergoing Watchman implantation	2.4 ± 1.2		Warfarin plus ASA for 45 days, DAPT for 6 months, and ASA for life	PROTECT AF protocol	PROTECT AF protocol	95%	25.4 ± 10.0	95%	2	
ASAP registry	150	150/0	Treat patients contraindicated for warfarin	2.8	4.4 ± 1.7	DAPT for 6 months and ASA for life	Stroke rate per 100 patient-years		95%		100%	2	
PREVAIL	407	269/138	Similar to PROTECT AF with revised inclusion criteria	2.6 ± 1.0		Similar to PROTECT AF	Stroke, embolism or unexplained death	Same as PROTECT AF within 7 days	95.1%		Modelled to 18 months; only 58 actually reached 18 months	1	4

Table 2: ACP registries in comparison with PROTECT AF.

Registry	Patients	Mean age (year 5)	Mean CHADS2 score	In-hospital Technical success	Stroke	Pericardial effusion conservative	Tamponade (drainage)	Device embolization	Death (all causes)	Total adverse events	Follow-up Device embolization	Pericardial effusion	Thrombus on device	Stroke	Death
Italian Registry	100			100/100 100%	0		2/100 2%	0	0	2/100 2%					
Dual Centre Hamburg Bern	131			131/131 100%	0	1/131 1%	0	0	0	1/131 0.8%					
ACP EU Post Market Registry	204	74 ± 9	2.6 ± 1.3	197/204 97%	0		3/204 1.5%	3	0	6/204 2.9%	1	0	5/204 2.4%		
Spanish Registry	35	75 ± 6	2.4 ± 1.3	34/35 97%	0	0	0	0	0	0	0	0	5/35 14%	1/35 3%	3/35 9%
Initial European Experience	143	74 ± 9	—	132/137 96%	3/143 2.1%	4/143 3%	5/143 3.5%	2/143 1.4%	0	10/143 7%					
Bern LAA Occlusion Registry	100	72 ± 10	2.5 ± 1.3	98/100 98%	1/100	2/100 2%	1/100 1%	2/100 2%	0	6/100 6%					
Initial Asian Experience	20	68 ± 9	2.3 ± 1.3	19/20 95%	0	0	0	0	0	*	—	—	—	—	—
Canadian Registry	52	74 ± 8	3 (2–4)	51/52 98%	0	1/52 2%	1/52 2%	1/52 2%	0	2/52 4%	0	1/52 2%	0	1/52 2%	3/52 6%
PROTECT AF	463	72 ± 9	2.2 ± 1.2	408/463 88%	5/463 1%	8/463 1%	22/463 5%	3/463 1%	0	36/463 8%	2/463 0.4%	0		16/694 2.3%	21/705 3.0%

*: Air embolism in right coronary artery, one esophageal injury during TOE.



(a) (b)

Figure 4: Left atrial appendage thrombosis (arrow), as seen with transesophageal echocardiography (a) and CT scan (b).

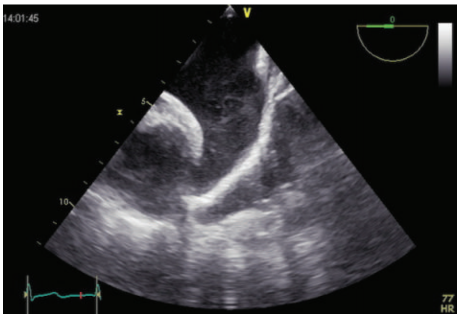


Figure 5: Severe spontaneous smoke effect (sludge) in left atrial appendage.

It has to be kept in mind that 2D TEE underestimates true dimensions in comparison to 3D TEE or CT measurements (Figure 6(b)) [58].

The maximal width of the LAA ostium is measured from the level of the left circumflex coronary artery up to a point at 1-2 cm from the tip of the left superior pulmonary vein limbus.

The maximal depth is measured from the ostium line to the apex of the LAA. Sizing tables are available for both the Watchman and ACP devices.

The size of the chosen device should at least be 10–20% larger than the measured diameter: a correct oversizing is essential in order to avoid peridevice flow after deployment; on the other side, excessive oversizing may result in a compression of the left circumflex artery.

It is worth noting that the ostium of the LAA is typically elliptical, while all available occluders have a round shape, possibly accounting for incomplete sealing of the device and possible cause of leakages.

ACP has to be preferred if the depth of the LAA is smaller than the width of the ostium, because the placement of a Watchman device may result in an unstable position.

Preprocedural TEE evaluation could also be useful to better assess the thromboembolic risk of the patient. LAA dimensions, LAA velocities, left atrial dimensions and fibrosis, left ventricular dysfunction, spontaneous echo-contrast, and aortic plaque (especially in aortic arc) have been associated with an increased thromboembolic risk [59]. In particular, the presence of left atrial abnormalities is associated with an embolic risk of 7.8%/year, as well as a CHA2DS2-VASc score of 5.

All these data could be useful to guide decisions on thromboembolic risk prevention in case of borderline CHA2DS2-VASc scores.

4.2. Procedural Imaging to Guide Left Atrial Appendage Occlusion. TEE allows us to visualize the LAA during the procedure: it is essential for the positioning and deployment of the device.

The majority of centers perform the procedure under general anesthesia with TEE and fluoroscopic guidance. There are only few reports of intracardiac echocardiographic guidance during percutaneous LAA occlusion.

TEE facilitates the transseptal puncture (Figure 7) and especially 3D TEE can provide a real-time full view of the LAA, the shape of the ostium (Figure 8), with accurate measurements of the landing zone.

A final decision on device size is based on the information collected with all imaging modalities: echocardiography, fluoroscopy, and CT.

After deployment, a tug test should be performed demonstrating simultaneous movement of the device and appendage (Figure 9). Optimally, the device should not protrude >4–7 mm beyond the LAA ostium, and residual flow should be <5 mm by color Doppler with a compression grade of 8–20%, expressed in percent comparing the diameter of the implanted device with the unconstricted diameter indicated by the manufacturer. When optimal positioning is confirmed, the device is released. Rare device embolization after mobilization of the patient has been observed.

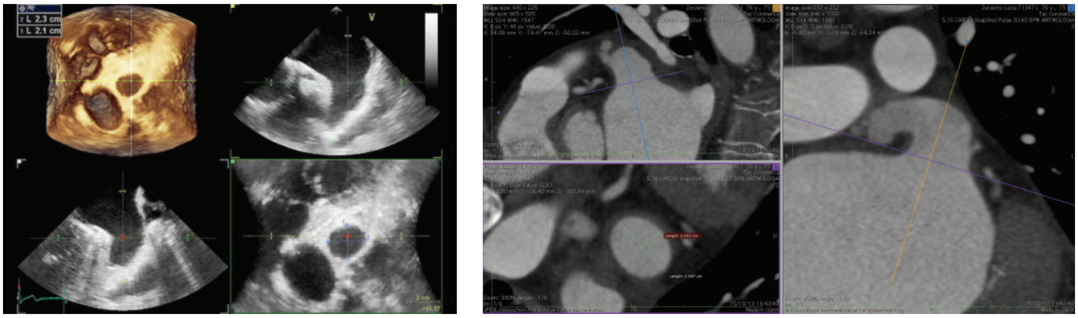
Following successful device deployment, the pericardium is evaluated for effusion.

4.3. Follow-Up Imaging. Postprocedural imaging aims to assess device position, peridevice residual flow in the LAA, and thrombus formation on the device.

TEE (Figure 10) and CT can both be used for this purpose.

In the PROTECT AF trial, serial TEE imaging was performed at 45 days, 6 months, and 1 year following implant [38].

Residual peridevice flow is common (41% at 45 days) in patients treated with the Watchman device. It is unclear if this



(a) (b)

Figure 6: Left atrial appendage measures with transesophageal echocardiography (a) and CT scan (b).

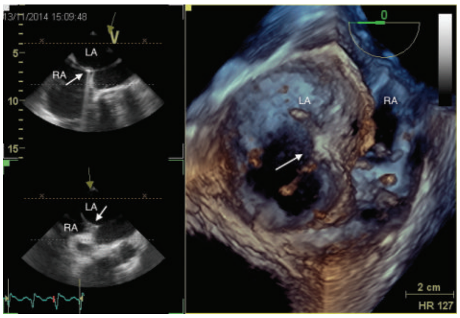


Figure 7: Real-time 3D echocardiography during transseptal puncture. The tip of the catheter (arrow) is passing from the right atrium (RA) to the left atrium (LA), through interatrial septum.

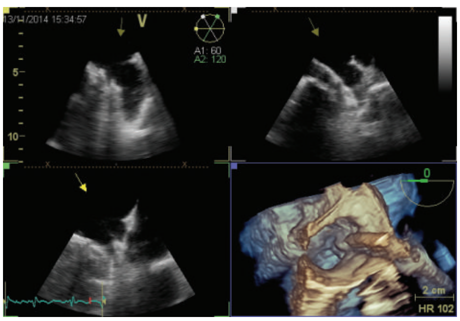


Figure 8: Progress of the delivery system in the left atrial appendage.

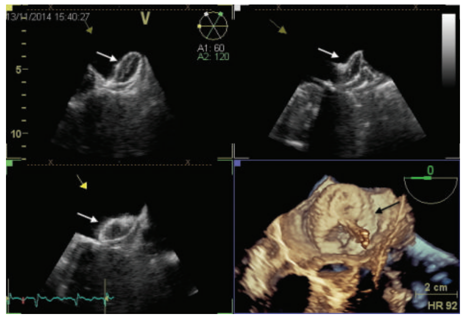


Figure 9: The image shows the so-called "tug test." An Amplatzer Cardiac Plug is pulled before the deployment. During this maneuver, the distal part of the device ("disk," arrow) is put in tension, while the distal part ("lobe") remains anchored in left atrial appendage.

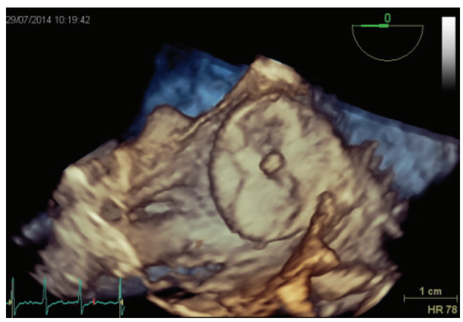


Figure 10: An Amplatzer Cardiac Plug six months after implant, with perfect sealing and endothelization.

could be related to possible thromboembolic events, since new thrombi may be formed in the distal LAA pouch [48]. Of note in the PROTECT AF trial, patients with a peridevice flow did not have a worse clinical outcome, regardless of the chosen antithrombotic therapy (warfarin, double antiplatelet agents, ASA).

With Amplatzer devices, as the disc of the device typically covers the entire LAA ostium (pacifier principle), residual peridevice leaks are less frequent.

4.4. Anticoagulation after Implantation. Postprocedural antithrombotic therapy with warfarin or dual antiplatelet drugs is recommended after implantation to avoid thrombus formation on the device until completion of endothelialization, provided there are no contraindications. For the Watchman device, the antithrombotic protocol of the PROTECT AF trial is adopted: 45 days after implantation warfarin was discontinued and substituted by ASA + clopidogrel if the TEE showed the absence of thrombi or a residual peridevice flow of <5 mm in width; clopidogrel was stopped if the 6 months TEE follow-up demonstrated no complications.

Usually, one antiplatelet agent is continued indefinitely, as most patients are elderly with evidence of atherosclerotic disease, although the bleeding risk must be considered.

The PREVAIL trial and ASAP study provided evidences for double antiplatelet therapy instead of VKA for the Watchman device.

Observational studies with the ACP followed a regimen of clopidogrel + ASA for 1 month and acetylsalicylic acid for 3 to 6 months [60], borrowing the antithrombotic protocol from the experience with the Amplatzer PFO Occluder. In patients who are treated with antiplatelets drugs, it is reasonable to perform an imaging test (TEE or CT scan) before clopidogrel termination and again if ASA cessation is planned.

Incomplete LAA occlusion could create, theoretically, a thrombus-containing pocket with a source of possible systemic embolization. Anyway, as mentioned above, small residual shunts (<5 mm) are usually considered irrelevant and may close spontaneously with time. When all patients with residual shunts are included, the stroke risk is no different compared with patients in whom the LAA is completely occluded regardless of antithrombotic therapy [48]. However, this remains a field open for debate.

5. Indications for Left Atrial Appendage Occlusion

PROTECT AF and PREVAIL randomized controlled trials were included in the recent ESC focused guidelines on stroke prevention in patients with atrial fibrillation. In fact, they suggest to use the CHA2DS2-VASc risk score >1 as the threshold value for considering LAA occlusion [16].

Individual risk-benefit evaluation is fundamental, bearing in mind that the use of OAC has a primary recommendation.

5.1. When Anticoagulation Is Not Possible. Patients with a high thromboembolic risk (CHA2DS2-VASc score of ≥2) but contraindication to systemic anticoagulation (e.g., history of intracranial or life threatening bleeding, coagulation disorders) represent the most accepted indication for LAA occlusion. In a survey of European centers, the most common indication for LAA closure was an absolute contraindication to OAC [61].

So far, no randomized trials targeting this specific group of patients are available; in fact, this is the result of several observational studies and registries. However, the significant bleeding risk of dual antiplatelet therapy, indicated for 1 or 6 months after implantation, has to be considered [62]. Generally, this is only for a short time, thus reducing the cumulative risk of major bleeding events.

In patients who cannot receive any antiplatelet agent, the Lariat technique can be considered.

5.2. When Oral Anticoagulation Is Possible. This is the only indication, as cited above, that is based on randomized controlled trials. Those patients, in whom OAC or NOAC are considered to pose an unacceptable bleeding risk (HAS-BLED ≥ 3), but with high stroke risk (CHA2DS2-VASc score of ≥ 2), should be considered for LAA occlusion.

The possibility of LAA occlusion should be discussed with the patient, remembering that anticoagulation currently remains the standard of therapy.

Patients should be elucidated about the possibility of therapy with NOAC, that, compared to OAC, have at least an equivalent and probably improved efficacy, with lower rate of intracranial and, for some, lower overall bleeding risk.

It should be emphasized that we do not have any direct data comparing NOAC with LAA occlusion.

Ultimately, the decision belongs to a well-informed patient in collaboration with the physician.

The HAS-BLED score does not characterize the bleeding risk in certain categories of patients (e.g., patients with cancer or chronic inflammatory bowel disease): to these, LAA occlusion may also be offered.

Another possible scenario in which LAA occlusion could be helpful is the setting of triple anticoagulant therapy due to coronary stent interventions in AF patients as it poses a significant rise in bleeding risk [63].

End-stage renal failure poses patients at a high stroke risk and high bleeding risk: LAA occlusion could be a debatable alternative, keeping in mind that all NOAC are contraindicated with creatinine clearance < 15 mL/min and warfarin could increase tissue calcification and enhanced atherosclerosis in this setting.

5.3. As a Complement to Anticoagulation. The combination of LAA occlusion and OAC is debated and occasionally performed in patients with embolic events despite the adequate antithrombotic therapy, provided that there are no other plausible causes (e.g., patients with mechanical prosthetic valves with evidence of thrombus in the LAA).

6. Conclusions

The LAA is considered the "most lethal human appendage" as it causes significant mortality and morbidity in AF patients. We have to learn more about its complex role in physiology and pathology.

However, LAA occlusion is becoming an interesting tool in reducing thromboembolic risk in certain categories of patients, as it has become a safe and effective procedure.

Indeed, we need new randomized prospective trials comparing LAA procedure with NOAC, as they have a safety profile better than old OAC.

Other interesting aspects that warrant investigation are the clinical significance of residual peridevice flow and the correct antithrombotic therapy after LAA closure.

In this way, we can shed light on thromboembolism management in AF, in order to improve our knowledge when choosing between different measures to reduce the risk of catastrophic strokes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Surgical Left Atrial Appendage Exclusion Does Not Impair Left Atrial Contraction Function: A Pilot Study

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Background. In order to reduce stroke risk, left atrial appendage amputation (LAAA) is widely adopted in recent years. The effect of LAAA on left atrial (LA) function remains unknown. The objective of present study was to assess the effect of LAAA on LA function. *Methods*. Sixteen patients with paroxysmal AF underwent thoracoscopic, surgical PVI with LAAA (LAAA group), and were retrospectively matched with 16 patients who underwent the same procedure without LAA amputation (non-LAAA group). To objectify LA function, transthoracic echocardiography with 2D Speckle Tracking was performed before surgery and at 12 months follow-up. *Results*. Mean age was 57 ± 9 years, 84% were male. Baseline characteristics did not differ significantly except for systolic blood pressure ($p = 0.005$). In both groups, the contractile LA function and LA ejection fraction were not significantly reduced. However, the conduit and reservoir function were significantly decreased at follow-up, compared to baseline. The reduction of strain and strain rate was not significantly different between groups. *Conclusions*. In this retrospective, observational matched group comparison with a convenience sample size of 16 patients, findings suggest that LAAA does not impair the contractile LA function when compared to patients in which the appendage was unaddressed. However, the LA conduit and reservoir function are reduced in both the LAAA and non-LAAA group. Our data suggest that the LAA can be removed without late LA functional consequences.

1. Introduction

Atrial fibrillation (AF) has a major impact on health care in the Western population and is associated with poor prognosis [1–3]. Besides widely adapted catheter ablation strategies for AF, an emerging treatment strategy is surgical PVI [4, 5]. One of the supposed advantages of this surgical approach is that the LAA can be excluded to reduce stroke risk [6]. Although beneficial effect on morbidity and mortality has not clearly been demonstrated, the LAA is amputated or closed by a clip on a large scale in stand-alone or concomitant AF surgery [7–9]. The effect of this amputation on left atrial function has not been addressed in the current literature.

Current echocardiography guidelines actively recommend the evaluation of LA function after AF to predict the maintenance of sinus rhythm and also identify patients at risk for LA failure or arrhythmias [10]. To assess this left atrial function, recent techniques have been introduced such as two-dimensional speckle tracking echocardiography (2D STE), specifically the parameters strain and strain rate [10, 11]. These novel strain parameters aid to assess the different left atrial functional stages: the reservoir function (storage of PV inflow during ventricular systole), conduit function (passive emptying during early diastole), and contractile function (active emptying at late diastole) [11, 12]. The aim of this study was to investigate the effects of left atrial appendage amputation on left atrial function in the setting of minimally invasive surgical PVI.

2. Material and Methods

2.1. Patient Population. This observational and retrospective matched group comparison was performed on two series of consecutive patients who were treated for drug resistant paroxysmal AF with sPVI between June 2009 and November 2011 in two centers: Academic Medical Center (AMC), Amsterdam, and University Medical Center Groningen (UMCG) [13]. Patients were matched for gender, age, LA diameter, and AF duration. Inclusion criteria were highly symptomatic paroxysmal AF without concomitant cardiac structural disease, refractory to class I and/or class III AADs or failed catheter ablation for AF. Exclusion criteria for surgical PVI were as follows: left atrial size > 60 mm (parasternal echocardiographic view), prior heart or lung surgery, significant coronary disease or previous MI, left ventricular hypertrophy > 12 mm, previous hospitalization for heart failure, moderate or severe mitral or aortic valve disease, or lung disease (prior tuberculosis or COPD Gold classes III-IV). Furthermore, patients with an ejection fraction < 50% were excluded. Patients in AF or atrial flutter at the time of the echocardiographic analysis were excluded since sinus rhythm is mandatory to reliably objectify the different phases of left atrial function. Definitions of AF, adverse events, and follow-up monitoring were based on the Heart Rhythm Society Consensus Statement for the catheter and surgical ablation of AF [14]. Patients provided written informed consent to the procedure. All patients were treated according to the standard of care for surgical PVI procedures in both AMC and UMCG, and no additional examinations were performed. Clinical and echocardiography data was collected retrospectively and patient privacy was granted by coding of the database according to the rules of good clinical practice and Dutch privacy law. Furthermore, all echocardiography files were anonymized before analysis at the University Medical Center Groningen, Netherlands.

2.2. Surgical Procedure. All patients were treated using the video assisted, completely thoracoscopic approach, as detailed previously by Krul et al. [15] and De Maat et al. [13]. In brief, the pulmonary veins were targeted by bilateral thoracoscopy. To isolate the pulmonary veins, a bipolar radiofrequency clamp (Isolator, AtriCure, Inc., Cincinnati, Ohio) was used to create a linear, transmural, thermal lesion. Following the ablation, measurement of effective conduction block was performed by pacing within the PVs (exit block). In the AMC series, also entry block was checked. No additional linear ablations (ablation lines) were applied on the atria. After effective isolation of both right and left PVs, the left atrial appendage was addressed. Concerning the left atrial appendage (LAA) management, in all patients from the LAAA group (AMC) the LAA was amputated with an endoscopic stapling device (Endo Gia stapler, Tyco Healthcare Group, North Haven, CT) [15], whereas in the non-LAAA (UMCG) group the appendage was intentionally not addressed [13].

2.3. Echocardiographic Analysis. For this study, a protocol for transthoracic echocardiographic measurement was compiled. In both centers, all patients underwent the echocardiographic analysis performed by experienced sonographers following the protocol. Complete set of measurements are described in Table 2. All images were stored digitally in a DICOM format and stored for offline analysis. Offline analysis was performed by an experienced sonographer (YMH) who was blinded for all other subject characteristics including surgical procedure (LAAA or non-LAAA group). Standard 2D measurements were performed using EchoPac BT12 (General Electric, Horton, Norway); 2D STE software was utilized to analyze LA deformation. All measurements were performed in accordance with the current echocardiographic recommendations and guidelines [10, 11]. Volumetric calculation of both LV and LA was performed using Simpson's biplane method of discs. Additionally LA end systolic volume was indexed to body surface area. Left atrial ejection fraction was calculated as $((\mathrm{LAV}_{\max} - \mathrm{LAV}_{\min})/\mathrm{LAV}_{\max}) * 100$ [16].

2.4. Two-Dimensional Speckle Tracking Echocardiography. For the strain measurements, the apical four-chamber view was utilized. As depicted in Figure 1, the edge of the LA endocardium was manually traced after which the software automatically generated tracings based on the speckles of the 2D image. The tracing was all inspected for correctness and manually adjusted if needed and accepted if tracing was acceptable. The software then calculated the mean deformation (strain) expressed in a percentage and speed of deformation (strain rate) expressed as 1/s of the speckles within the region of interest.

As described previously [11, 12], the left atrial function can be divided into three phases. For strain measurements, these are defined as follows: (1) *reservoir function* was calculated as maximal LA wall deformation during LV systole as compared to the preset reference point (end diastole); (2) *conduit function* is considered the maximal LA wall deformation during early LV diastole; and (3) *contractile function* is considered as the maximal LA wall deformation during late LV diastole (after the P wave on ECG). Consecutively, strain rate could be calculated in these three different domains: reservoir, conduit, and contractile function. To determine the effect of the LAAA compared to the non-LAAA group, the delta (before surgery to follow-up difference) of all parameters was compared between groups.

2.5. Follow-Up. All patients visited the outpatient clinics according to standard institutional protocol of care for patients treated for AF and underwent a protocolled echocardiogram before surgery and at a median of 12 months (range 6–24 months) after surgery. Periprocedural adverse events were registered. Due to the observational nature of the study, no further specific investigation was requested from the patients.

2.6. Endpoints. The primary endpoint was atrial function as evaluated by strain, strain rate, and left atrial ejection fraction, compared between groups. Secondary endpoints were LAAA

Table 1: Baseline characteristics.

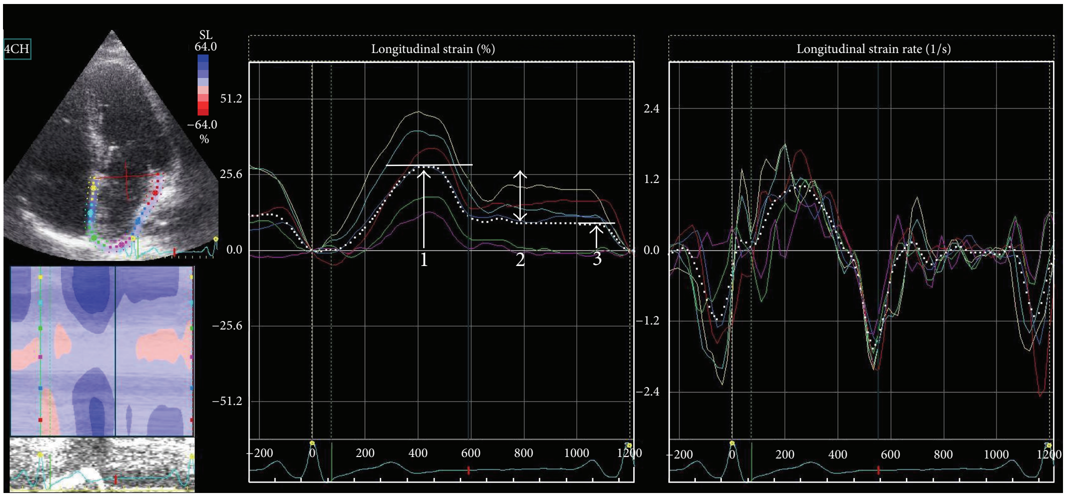
	Non-LAAA group (n = 16)	LAAA group (n = 16)	p value
Age, years	54 ± 10	59 ± 8	0.07
Male, n (%)	14 (88%)	13 (81%)	0.63
Median AF history, years [range]	3 [1–10]	4 [1–15]	0.15
AF type			
Paroxysmal, n (%)	16 (100%)	16 (100%)	
Previous catheter PVI, n (%)	0 (0%)	1 (6%)	0.31
Catheter CTI ablation, n (%)	1 (6%)	0 (0%)	0.31
CHA_2DS_2-VASC			0.14
0, n (%)	7 (44%)	6 (38%)	
1, n (%)	7 (44%)	2 (12%)	
≥2, n (%)	2 (12%)	8 (50%)	
Body mass index (kg/m^2)	28 ± 4	27 ± 3	0.47
Body surface area (m^2)	2.15 ± 0.18	2.10 ± 0.23	0.47
Hypertension, n (%)	4 (25%)	7 (44%)	0.26
Diabetes, n (%)	0 (0%)	1 (6%)	0.31
Stroke history, n (%)	0 (0%)	2 (12%)	0.14
Systolic blood pressure (mmHg)	124 ± 19	142 ± 14	**<0.01***
Diastolic blood pressure (mmHg)	83 ± 18	82 ± 11	0.76
Heart rate (beats/min)	60 ± 9	64 ± 17	0.37
Echocardiography			
LV ejection fraction (%)	59 ± 5	60 ± 7	0.90
LA ejection fraction (%)	40 ± 7	37 ± 10	0.41
LA diameter (mm)	42 ± 6	43 ± 6	0.61
LA volume (mL)	75 ± 15	89 ± 30	0.11
LA volume indexed (mL/m^2)	35 ± 5	42 ± 11	0.06
LA strain measurements (%)			
Reservoir function	29.2 ± 7.3	23.1 ± 7.6	**0.03***
Conduit function	16.1 ± 6.0	12.1 ± 4.9	**0.05***
Contraction function	13.2 ± 4.8	11.0 ± 5.0	0.22
LA strain rate measurements (s^{-1})			
Reservoir function	1.15 ± 0.35	0.92 ± 0.19	**0.03***
Conduit function	−1.20 ± 0.45	−0.97 ± 0.29	0.09
Contraction function	−1.42 ± 0.46	−1.13 ± 0.44	0.08

* p-value ≤ 0.05.

Table 2: Primary endpoints.

Parameter	LAAA group baseline	LAAA group follow-up	p value within group	Non-LAAA group baseline	Non-LAAA group follow-up	p value within group	Δ between groups
Parasternal LAD (mm)	43 ± 6	43 ± 4	0.53	42 ± 6	44 ± 5	0.30	0.16
LAEF (%)	37 ± 10	37 ± 12	0.92	40 ± 7	37 ± 12	0.64	0.72
LAVI (LAV/BSA)	42 ± 11	41 ± 12	0.74	36 ± 5	36 ± 9	0.77	0.53
Strain reservoir (%)	23.1 ± 7.6	17.1 ± 4.6	**<0.01***	29.2 ± 7.3	23.6 ± 6.3	**<0.01***	0.70
Strain conduit (%)	12.1 ± 4.9	8.2 ± 3.5	**0.01***	16.1 ± 6.0	11.6 ± 5.2	**0.02***	0.47
Strain contraction (%)	11.0 ± 5.0	8.2 ± 3.3	0.07	13.2 ± 4.8	12.1 ± 4.1	0.15	0.18
Strain rate reservoir (s^{-1})	0.92 ± 0.19	0.79 ± 0.19	**0.03***	1.15 ± 0.35	0.92 ± 0.31	**0.02***	0.29
Strain rate conduit (s^{-1})	−0.97 ± 0.29	−0.78 ± 0.35	0.11	−1.20 ± 0.45	−1.01 ± 0.35	0.053	0.94
Strain rate contraction (s^{-1})	−1.13 ± 0.44	−0.93 ± 0.36	0.09	−1.42 ± 0.46	−1.27 ± 0.41	0.11	0.72

BSA = body surface area, LA = left atrium, LAEF = left atrial ejection fraction, LAD = left atrial diameter, PVF = pulmonary vein flow, LAV = left atrial volume, LAVI = left atrial volume indexed, * p value ≤ 0.05.



(1) Reservoir function was measured as maximal LA wall deformation during LV systole as compared to the preset reference point (end diastole)
(2) Conduit function is calculated as difference between measurement 1 and 3
(3) Contractile function was measured as the maximal LA wall deformation during late LV diastole (after the P wave on ECG)

Figure 1: Strain and strain rate measurements.

related adverse events and rhythm outcome at 12-month follow-up without antiarrhythmic drugs.

2.7. Statistics. Baseline descriptive statistics are presented as mean ± standard deviation or median (range) for continuous variables, as appropriate, and counts with percentages for categorical variables. Differences between subgroups, in terms of patient characteristics at baseline, different follow-up moments, and end of study, were evaluated by Student's t-test or the Mann-Whitney U test, depending on normality of the data. Differences within subgroups were evaluated using the Paired t-test. Chi-square or Fisher's exact test was used for comparison of categorical variables. The statistical software package IBM SPSS Statistics version 22 was used for all analysis.

3. Results

3.1. Patient Population. A total of 32 patients were treated with sPVI for lone, drug refractory AF. Mean age was 57 ± 9 years; 84% were male. Paroxysmal AF was present in all 32 patients (100%) and the median AF duration was 3.5 years (range 1–15). In the non-LAAA group 2 (13%) patients had a CHADS2VASC score ≥ 2; in the LAAA group this number was 8 (50%). Two patients underwent previous transcatheter ablation; one patient underwent a cavotricuspid isthmus ablation for a right-sided flutter; another patient underwent transcatheter PVI for AF. The mean systolic and diastolic blood pressure was 134 ± 19 and 82 ± 15 mmHg, respectively. The mean heart rate was 61 ± 10 beats per minute. Baseline clinical patient characteristics did not differ significantly between the two groups except for systolic blood pressure ($p = 0.005$) (Table 1). Before surgery, ventricular diameters, volume, and ejection fraction were similar between groups. The left atrial indexed volume was enlarged with 42 ± 11 in the LAAA group versus 36 ± 5 in the non-LAAA group ($p = 0.06$). Before surgery, strain rate reservoir function differed significantly between groups ($p = 0.026$), but the strain rate conduit and contraction function did not differ between groups ($p = 0.086$ and $p = 0.079$, resp.) (Table 1).

3.2. Surgical Treatment. In all patients, the sPVI procedure was completed with proven acute block. Mean procedural time was 160 ± 60 minutes. Mean hospitalization was 7 ± 2 days. The LAA was successfully excluded in all 16 patients in whom LAA amputation was planned. This was objectified by TEE after amputation of the LAA. No periprocedural bleedings and, specifically, no LAAA related bleedings were observed.

3.3. Left Atrial Function

3.3.1. LAAA Group. At a median of 12-month follow-up echocardiography, the LA diameter and volume indexed to BSA, in the LAAA group, was unchanged compared to baseline measurements ($p = 0.530$, $p = 0.646$, and $p = 0.735$, resp.). Compared to baseline, the strain measured at follow-up of the reservoir and conduit but not contractile phase had decreased (with $p = 0.007$, $p = 0.014$, and $p = 0.070$, resp.). In the strain rate domain, the reservoir function decreased accordingly, but this was not observed in the conduit and contractile phases (with p values of 0.029, 0.109, and 0.092, resp.) (Table 2 and Figure 2).

3.3.2. Non-LAAA Group. At follow-up echocardiography, the LA diameter and left atrial volume index of the LAAA group was unchanged compared to baseline measurements ($p = 0.301$, $p = 0.478$, and $p = 0.773$, resp.). Compared to baseline, the strain at follow-up had decreased in reservoir and conduit but not in contractile function ($p = 0.001$, $p = 0.017$, and 0.151, resp.). The strain rate of the reservoir

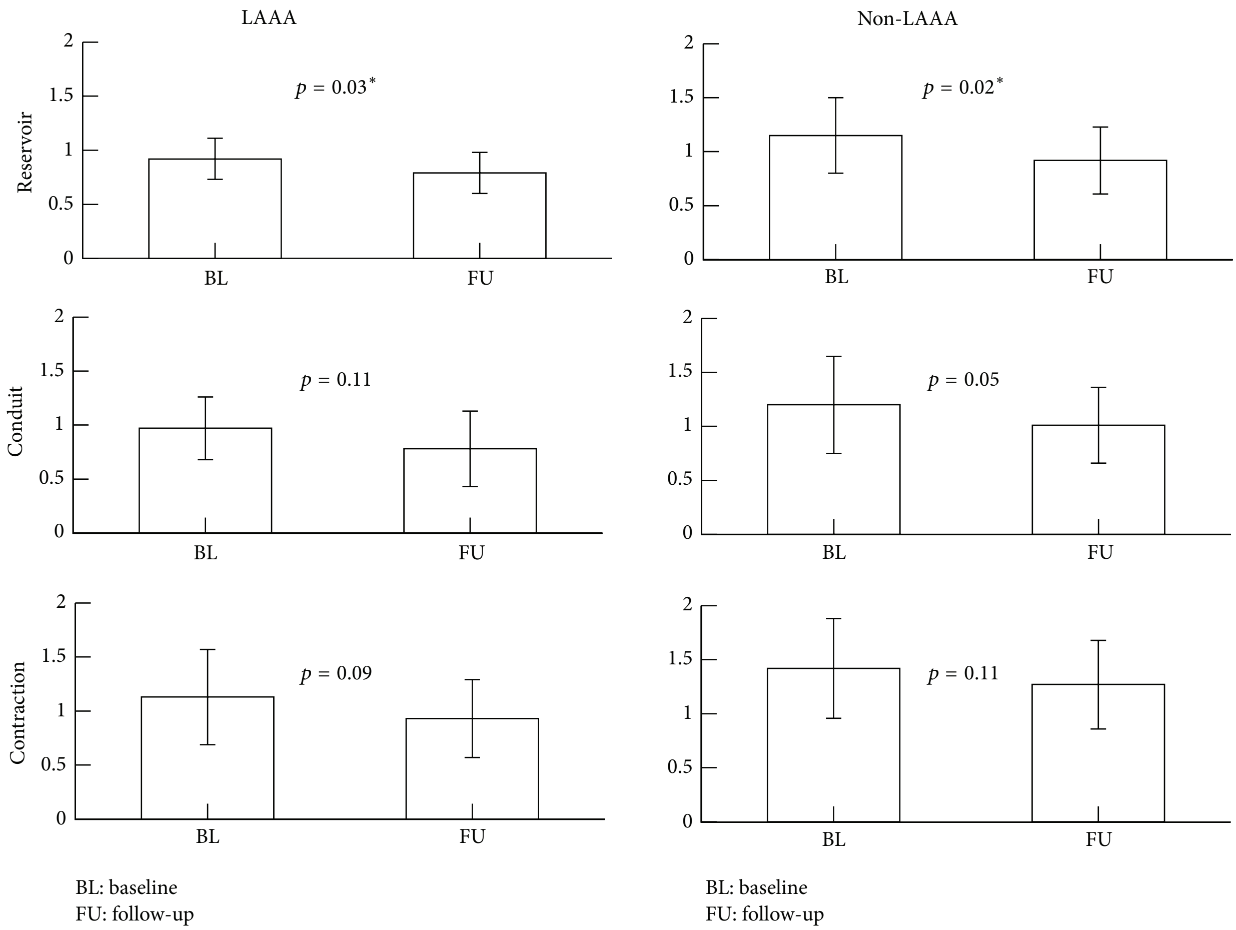


Figure 2: Strain rate bar graph.

function decreased significantly whereas conduit and contractile function did not, with p values of 0.019, 0.053, and 0.108, respectively (Table 2 and Figure 2).

3.3.3. Comparison between Groups. When the delta (difference before surgery and follow-up measurements) is compared between the LAAA and non-LAAA group, none of the changes in atrial dimensions, atrial function, strain, or strain rate measurements differed significantly (Table 2). Left atrial ejection fraction did not differ significantly, neither within nor between groups.

3.4. Follow-Up, Procedural Safety, and Rhythm Outcome. Of all patients, pre- and postoperative echocardiography were available and no patients were lost to follow-up. Echocardiography was conducted after a median of 12-month (range 6–24) follow-up. In the LAAA group, no periprocedural (LAA) bleeding occurred. In both investigated groups, 15 (94%) patients were free from atrial arrhythmia and antiarrhythmic medication at 12-month follow-up.

4. Discussion

In this retrospective, observational matched group comparison with a convenience sample size of 16 patients, the findings suggest that amputation of the left atrial appendage does not impair the contractile left atrial function or left atrial ejection fraction in patients without structural heart disease. However, the LA reservoir and conduit functions were impaired significantly in both groups at follow-up echocardiography.

Literature does not report the actual contribution of the left atrial appendage to the atrial function or more specifically the contraction. Our study shows that the amputation of the LAA does not significantly affect the left atrial contraction. Our findings contrast with the previous report of Gelsomino et al. who describe improved atrial function and reverse remodeling after successful sPVI [17]. Left atrial volume reduced significantly in these patients, whereas in our group the dimensions did not. This difference might be explained by the more extensive lesion set applied in the series of Gelsomino et al., resulting in more scar related contracture leading to a decrease in left atrial volume [17, 18]. Also, in that series, 49% of patients underwent LAAA or closure; in the other 51% the LAA was not addressed.

It is remarkable that the LA reservoir and conduit function are impaired in both groups following minimally invasive sPVI; this has not been reported previously and might be contributable to the postoperative adhesions of the pericardium and/or antral scarring due to the ablation. Furthermore, it could be hypothesized that this impaired passive left atrial function (conduit and reservoir) precedes active (contractile) left atrial function impairment, as observed in the left ventricle. More research on this topic is warranted.

In our patient population, the rhythm outcome was excellent. This is contributable to our selected, relatively young and healthy patient population with a short history of highly symptomatic paroxysmal atrial fibrillation. Our results are in accordance with the current literature on sPVI procedures [19, 20]. In the present series, no periprocedural bleeding was observed and, specifically, no LAAA related bleedings. This notwithstanding, LAAA related bleedings have been reported, due to the fragile and delicate wall of the LAAA [21, 22].

It has previously been demonstrated that the left atrial appendage is responsible for atrial natriuretic factor (ANF) and performs an important physiologic function regulating the intravascular volume via release of atrial natriuretic peptide. In normal hearts, 30% of the ANF is contained in the LAA. With appropriate medical therapies, postoperative hypertension can be adequately managed, without residual long-term hemodynamic effects.

For this study, we objectified the different left atrial phases by tissue velocity imaging, speckle tracking method. This technique was originally introduced to study left ventricular function. As a spin-off, this technique has been applied to the left atrium and several groups have showed feasibility and good reproducibility in the setting of speckle tracking on the left atrium [11, 23, 24]. As described, this method provides new and interesting information on the left atrial function, specifically reservoir, conduit, and contractile function. However, it remains unclear in what quantities the reservoir, conduit, and contractile phase contribute to the ventricular filling. It also remains unknown what the clinical effect of reduced conduit and reservoir function is, especially in our specific young patient population without major comorbidity. Further study is warranted on the subject of left atrial function, both in healthy subjects and in the context of atrial fibrillation ablation.

5. Conclusions

In this retrospective, observational matched group comparison with a convenience sample size of 16 patients, the findings suggest that left atrial appendage amputation does not impair the contractile left atrial function when compared to patients in which the appendage was unaddressed. However, the left atrial conduit and reservoir function decreased in both LAAA and non-LAAA group following minimally invasive surgery for AF. Our data suggest that the LAA can be removed without late left atrial functional consequences.

Strengths and Limitations

Since a small number of patients were enrolled in this retrospective and observational study, no definite conclusions can be drawn. Although matching provided similar patient characteristics, there were differences between groups at baseline when regarding strain and strain rate. This is counterbalanced by the fact that consistent (echocardiographic) follow-up was conducted and that comparisons are conducted both between and within groups.

Disclosures

Dr. Stefano Benussi has a financial relationship with St. Jude Medical Inc., AtriCure Inc., Medtronic Inc., CryoCath Inc., and Edwards Lifesciences Inc. Dr. Joris R. de Groot and Dr. Antoine H. G. Driessen have a financial relationship with AtriCure Inc.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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