Multimodality Imaging for Best Dealing With Patients in Atrial Arrhythmias

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Running title: imaging and atrial arrhythmias

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HIGHLIGHTS

- Atrial anatomy and functions are key and should not be forgotten by imagers. There are key pathophysiological, prognostic and therapeutic values in analysing the left, and probably also the right, atria.
- Atrial volumes are important, atrial deformation during the reservoir and probably also during the active booster pump function have to be consider
- Cardiac CT but also cardiac magnetic resonance imaging have important roles, also for assessing atrial anatomy and for characterizing tissue and for guiding for treatment strategies.
- There are many proof-of concepts data, large prospective and interventional studies are up-to-now missing in that field of imaging the atria.

ABSTRACT
The management of atrial fibrillation (AF) is a clinical challenge but also an imaging challenge. The role of different imaging modalities to estimate the thrombo-embolic risk in AF is a key clinical question. The present review summarizes the advances of myocardial imaging in the stratification of, thromboembolic risk, diagnosis and management of left atrial thrombosis in patients with AF. These imaging techniques are also important for understanding arrhythmias and their consequences. It is becoming fundamental for guiding therapy. Still large studies are required but be sure that left atrial imaging will become more and more clinically fundamental.

Key Words
Atrial fibrillation, echocardiography, strain, cardiac magnetic resonance, electro-anatomic mapping

Abbreviation list:
LA: left atrial
AF: atrial fibrillation
LAA: left atrial appendage
TTE: transthoracic echocardiography
TEE: transesophageal echocardiography
PV: pulmonary vein
cMRI: cardiac magnetic resonance imaging
LGE: late gadolinium enhancement
CT: computed tomography
FIRM: focal impulse and rotor modulation
BIFA: box isolation of fibrotic areas

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a prevalence of approximately 3% in adults, which further increases with advancing age(1). The prevention and optimal management of AF patients will become fundamental with this expected increase in prevalence.

AF is independently associated with a 1.5- to 2-fold increased risk of all-cause mortality and increased morbidity in the general population(2).

Common cardiovascular risk factors, ischaemic cardiomyopathy, valvular heart disease, and heart failure are associated with left atrial (LA) dilatation and increased risk of developing AF(1-3). In this review, the role of multimodality imaging in the evaluation and treatment of AF is discussed.

Some pivotal questions remain and the lack of use of imaging techniques when deciding for the longtime prescription of anticoagulant therapy is reflecting the need for large studies involving imaging in trying to best manage patients with AF(4,5). Convincing data need to be collected but great value of a more systematic assessment of the LA should change the future management of AF (prevention and prevention of its complications).

Imaging and left atrial anatomy

The very last years have been characterized by a resurgence of interest in the left atrium (LA). This revival is probably due the prognostic impact of LA-size and function in different pathological conditions including valvular heart disease, heart failure and also AF(6-9). Moreover, the development of catheter ablation techniques has contributed to increase the awareness of the anatomical structure inside the LA. The LA is the most posterior of the cardiac chambers. Blood coming from the lung enters the posterior part of the LA by the four pulmonary veins, then passes in the vestibule (anterior wall), which is the outlet part of the atrial chamber surrounding the mitral orifice. The septal wall divides the LA from the RA: its anterior part is closely related to the aortic root through the transverse pericardial sinus, and the thin floor of the *fossa ovalis* allows direct access between the RA and LA during trans-septal puncture (Figure 1). The LA appendage (LAA) is a finger-like extension originating from the main body of the LA, between the anterior and the lateral walls. Different morphologies for the LAA appendage have been described, with “chicken wing” being the most common (48%), followed by “cactus” (30%), “windsock” (19%), and “cauliflower” (3%) The “cauliflower” morphology has been associated increase risk of embolic event(10). A "cauliflower" LAA, defined as a main lobe of less than 4 cm long without forked lobes, was significantly more common in patients with stroke(11,12). Others demonstrated that the number of lobe is the most important parameter of risk (13).

Because of anatomical constraints, LA dilatation is frequently asymmetrical and less pronounced in the anteroposterior direction. This is the reason why the estimation of LA volume by the Simpson’s rule or the area-length ellipsoid methods from bi-plane 4 and 2 chambers apical views at 2D-transthoracic echocardiography (TTE) is recommended and is the most reliable method to assess LA dimension(14). But, the application of geometrical assumptions (15), and foreshortening of atrial roof(16) lead to LA volumes measured at 2D-TTE that are often smaller than those reported from cardiac magnetic resonance imaging (cMRI) or computed tomography (CT)(17,18). It is important to encourage the use of LA 3D-volume in our routine clinical practice. LA-anatomy routine assessment can not be limited to a diameter or a surface-area. Geometry is becoming more and more important.

LA roof shape assessed by CT imaging (deep-V, shallow-V, or flat) can help determine the possible sites of AF triggers, as triggers from the PVs become less common at the LA roof shape flatten (19).

Being free from geometrical assumptions and foreshortening, real-time 3D echocardiography might be an attractive alternative for the evaluation of atrial volume. LA volumes measured by 3D-echocardiography are nearer to those obtained with cMRI and CT (18). Nevertheless, 3D echocardiography is still requiring a multi-beat acquisition (4 to 6 cardiac beats) and is therefore not suitable for patients in atrial fibrillation(20). .

The relationship between LA dilatation (defined by LA volume in end-systole) and AF occurrence is well known, and persists after correction for other risk factors as age, gender, valvular heart disease or hypertension(21). LA enlargement is associated with a greater electrical burden(22) and with a high thromboembolic risk as assessed by both CHADS2 and CHA2DS2-VASc scores(23).

However, the relationship between LA size and actual thromboembolic events is less well established(24). Some studies are reporting a significant association between LA-size and thromboembolic events(25) whereas other large trials failed to find a significant association between LA dimension and thromboembolic risk in AF(22,26). LA-volume is nowadays mainly considered in end-systole but there are studies in favor to the use of LA minimal volume (LA expansion index) (27,28).

Imaging and assessment of LA-thrombosis

Spontaneous echocardiographic contrast (SEC) or “smoke”(29) are ultrasound characteristic images that are reflecting the slowness of blood flow and the formation of blood cells aggregates. As stasis progresses, SEC becomes dense and with a viscid appearance, commonly called "sludge"(30). Sludge is often difficult to distinguish from thrombus, and probably represent an intermediate phase along the continuum towards thrombus formation. Compared to SEC and sludge, LAA thrombus has greater prognostic value with respect to the occurrence of thromboembolic events(31).

Transoesophageal echocardiography (TEE) is considered the gold-standard method for the detection of SEC or thrombus in the LA and LAA, with a specificity, sensitivity and accuracy of 100%, 93% and 99%, respectively(32). Recently, the use of 3D-TEE facilitates a multiplanar approach for the assessment of LAA and allows 3D reconstruction of the LAA short and long axis [figure 2]. In patients with LAA artifacts or significant SEC, the application of echo-contrast during TEE may be helpful to confirm/exclude the diagnosis of LA-thrombosis and improve the management of patients undergoing electrical cardioversion or AF-ablation(33). LAA-emptying velocity can be measured at TEE, by positioning the pulsed-Doppler wave cursor in the proximal third of the appendage. Velocities <40 cm/s are associated with a higher risk of stroke (30); velocities <20 cm/s are often associated with LA-thrombosis (34).

Cardiac CT is excellent for the assessment of pulmonary vein (PVs) anatomy and LAA size and morphology(35) before AF-ablation or LAA-occlusion. Fusion-imaging (CT +X-ray) or 3-D printing could be used in case of complex anatomy to choose the size of the prosthesis and verify its suitability. On the contrary, the role of cardiac CT in the assessment of LA thrombosis is limited by the occurrence of fillings defects in patients with significant LAA stasis, which increases the number of false positives and significantly reduces the PPV of this method(36). Two-phase ECG-gated CT with delayed acquisition might offer new insight into thrombus detection(37), whereas the analysis of aortic/atrial opacification helps differentiate LAA thrombus from artifact at CT(38). Another limit of cardiac CT for thrombus detection is the temporal relationship between the CT and procedure planned such that knowledge of lack of thrombus even 48 hours prior to a procedure in a persistent AF patient may not be sufficient to assume lack of thrombus at the time of a procedure and, contrarily to the ultrasound approach, CT is not measuring the LAA emptying flows that are associated with the thrombo-embolic risk. The applicability of cMRI in the detection of LA-thrombosis is limited by a reduced spatial resolution and susceptibility to slow-flow, which increases the number of false positives and reduces positive predictive value(39).

Assessment of LA function

Even if the guidelines on management of atrial fibrillation do not include the assessment of atrial function(4,40), there is now growing evidence supporting its use in the evaluation of patients with atrial fibrillation. Atrial function can be divided in three components: reservoir function, conduit function and booster pump function(41). Reservoir function corresponds to the collection of pulmonary venous flow during LV systole; conduit function is the passage of blood to the left ventricle during early diastole; and pump function is the active contraction of the atrium which contributes to LV filling in late diastole which is lost in case of atrial fibrillation. These different components of atrial function can be assessed using volumetric and speckle tracking technics.

Imaging techniques to assess atrial function

<u>Volumetric methods:</u>

Atrial dimensions vary widely during the cardiac cycle, therefore atrial functions can be quantified by measuring atrial volumes at different times during the cardiac cycle. The maximum volume is measured at the ventricular end-systole just before the atrioventricular valve opening (MaxAV); the pre-atrial contraction volume (PaAV) is measured at mid-diastole, just before atrial contraction; and the minimum volume (MinAV) at the LV end-diastole is measured just before the closure of the atrioventricular valve. The combination of these LA volumetric measurements allows the calculation of the three basic functions of the atria(41):

- Reservoir function: Atrial Emptying Fraction = (MaxAVi–MinAVi)/MaxAVi x100
- Conduit function: Passive Emptying Fraction = (MaxAVi–PaAVi)/MaxAVi x100 it can also be expressed as Conduit volume = (ventricular stroke volume index–[MaxAVi - MinAVi]).
- Booster pump function: Active atrial emptying fraction = (PaAVi–MinAVi)/PaAVi x100.

Speckle tracking techniques (or feature tracking in Cardiac-MR):

Myocardial strain imaging, which is widely used to assess ventricular function, has also been applied to assess atrial function (Figure 3). To date, it is still confined to the field of research and small sample size observational studies (42). During the reservoir phase, the atria are stretched as they fill with blood, therefore longitudinal atrial strain increases with a maximal positive peak reached at the end of the atrial filling. After atrio-ventricular valve opening, the atria empty quickly, leading to a decrease in atrial strain. This leads to a plateau corresponding to atrial diastasis. Finally, the atria will shorten during the atrial active atrial booster pump function, leading to a further decrease in strain (20,43). LA strain is a rapid, easy, and rather robust method for assessing LA-function(44). But, atrial strain assessment has some limitations. First of all, the thin atrial walls make strain more difficult to assess than with the left ventricle, that is also impacting part of LA-strain curves (45). The rather low level of evidence up to now and a lack of standardization is a weakness that is expected to be solved by ongoing efforts including the American Society of Echocardiography and European associations for cardiovascular imaging(46).

Atrial function in clinical practice for the assessment of patients with atrial fibrillation (table 1):

- ***Identification of patients at risk of atrial fibrillation:***

  Reduced reservoir and booster pump function were associated with an increased risk of new-onset AF in general or cryptogenic stroke population(47). An alteration in atrial function was also associated with AF in healthy athletes(48). Studies have demonstrated the relationship between LA strain, LA fibrosis and hospitalization, cardio-embolic events or AF (49-51).

- ***Prediction of success of AF reduction:***

Alteration in LA function is associate with an increased recurrence of AF after a first radiofrequency catheter ablation procedure (42,52,53). Therefore, atrial reservoir function might be used for best predicting the success-rate of the procedure and to individualize the follow-up.

- ***Prediction of stroke:***

LA strain has also been demonstrated to provide incremental diagnostic information over that provided by the CHA2DS2-VASc score, suggesting that LA strain analysis could improve the current risk stratification of embolism in patients with low CHA2DS2-VASc score (54,55).

In summary, atrial function (essentially LA reservoir function) is a predictor of AF-occurrence and recurrence, and its value seems to be associated with thromboembolic risk. LA strain (mainly using echocardiography but could also be obtained using the feature tracking and cardiac-MR technique) is a relevant approach that has been mainly evaluated for its reservoir component(56-60). Still, large randomized studies are needed to confirm whether atrial function can be used to risk-stratify patients(24,61).

Imaging and LA Appendage (LAA) closure

Because thromboembolism in AF typically arises from thrombi originating in the LAA, currently, several percutaneously delivered devices for LAA exclusion have been developed. Controversies are existing and the definition of the target population for these procedures remain debated. Percutaneous closure of LAA is supposed to be the treatment of choice for patients having a high-thromboembolic risk and demonstrated contraindication to anticoagulation(62-64). 2D- and 3D- transesophageal echocardiography has a crucial role in the pre- and post-procedural assessment and intraprocedural guidance of percutaneous LAA-occlusion procedures. Because currently available LAA occlude devices (Watchman®, Amplatzer®, Cardiac Plug®, and Amulet®) are delivered using peripheral venous access, the LAA can be reached only after trans-septal puncture, which is realized under careful transoesophageal guidance in inferior and posterior portion of the interatrial septum)(65-70). The inferoposterior puncture position allows the most direct route to the anterolaterally located LAA (figure 1). The presence of a large atrial septal aneurysm of lipomatous hypertrophy should be notified.

LAA anatomy is typically established during the screening process using TEE and gated cardiac computed tomographic angiography and should be confirmed during the procedure using both TEE and fluoroscopy.

The main parameters to be taken into account before LAA occlusions are: the characteristics of the LAA orifice (oval or irregular); the length and angulation of the LAA. The absence of thrombus, the pericardium should be checked as well as the location of the circumflex artery. L AA should be interrogated in the 0, 45, 90 and 135° views. Of note, the Amplatzer cardiac plug will be positioned at the neck of the LAA where the Watchman will be anchored in the ostium of LAA.

Of the known LAA variants, the chicken-wing morphology cause the greatest procedural difficulty with regard to LAA occlusion/exclusion, due to its broad width and shallow depth, which create a difficult situation regardless of the type of device used(71) (figure 2).

3D TEE is after LA pressure optimization, used in the cath-lab for finally deciding the size of the prosthesis. After the sizing, the positioning, the delivery and stability of the device is monitored by TEE and its 3D and biplane capabilities(71).

Imaging and atrial fibrosis

LA-fibrosis is characterized by myofibroblast proliferation and collagen deposition in the LA myocardium, and is responsible of anisotropy, disruption of normal conduction and re-entry circuits, which forms a substrate fostering AF (72). In parallel, AF leads to atrial structural remodelling characterized by disorganization of myocyte architecture and expansion of the extracellular matrix in the LA tissue, which promotes a vicious cycle perpetuating AF, even though the exact pathophysiology remains incompletely understood(73). Several studies have shown that the extent of LA fibrosis correlates with persistent rather than paroxysmal AF, detrimental outcomes such as strokes, and AF ablation failure or recurrence (74,75).

Magnetic resonance imaging and LA fibrosis

Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) has been so far, the main imaging method that enables detection, localization and quantification of LA fibrosis with fairly good histological correlates(76,77). Fibrotic changes within atrial tissue usually appear as thin areas of gadolinium enhancement predominating in the posterior LA wall(78) (Fig. 4A). Specialized image post-processing may allow the quantification of fibrotic changes, which may be expressed, either as a percentage of LA whole area, or through a volume rendering model showing the spatial extent of LGE(79) (Fig. 4B). However, the very thin LA wall requires high performance in terms of signal and spatial resolution, which necessitates specific – and currently non-commercially available – CMR pulse sequence. Moreover, patients' arrhythmia during acquisition can severely hamper image quality, leading to a substantial amount of non-diagnostic examinations. Therefore, due to technical challenges limiting its spread and routine use, LGE CMR of atrial fibrosis cannot be considered fully mature yet. But, this is an important "work-in-progress" image-based approach for best selecting and perhaps applying the ablative therapies (AF recurrence progressively increased as a function of LGE. LGE >35% have a higher rate of AF recurrence in the first year after ablation) (80).

T1 mapping is a neighbouring CMR approach, based upon the measurement of T1 relaxation times in each myocardium voxel in order to generate either post-contrast T1 or extracellular volume fraction maps(81). Two studies have shown that post-contrast T1 relaxation times measured in LA wall were shorter in patients with AF than in controls, indicating an expansion of extracellular matrix (82,83). In the study of Ling et al., post-contrast atrial T1 time correlated with tissue voltage and with arrhythmia recurrence after catheter ablation(82). By providing a voxel-based T1 value estimation of the whole LA, T1 mapping appears to be a more quantitative method than LGE imaging, however, it shares the same limitations in terms of spatial resolution. In addition, T1 mapping still faces critical issues related to standardization of methods and reproducibility of outcomes, despite the efforts to overcome them(84). Recently, CMR feature tracking imaging has been reported to quantify LA strain (table 1). Peak longitudinal strain of LA was found to correlate strongly with LA fibrofatty replacement at histologic analysis(85).

Not yet extensively available (lack of feasibility outside highly experimented centers, lack for standardization, still part of subjectivity in the analyses), Cardiac-MR and precise assessment of

LA-structure will lead to the emerging era of "mechanism-directed therapy". In the next future, patients with AF will become potential candidate for ablative therapy based on electrophysiological target that can be identified and therefore eliminated(86).

Imaging and Electrophysiology

Since the seminal demonstration from Haissaguerre et al (87)of the responsibility of PVs to trigger AF, catheter ablation has emerged as the gold standard treatment for rhythm management for patients with symptomatic paroxysmal or persistent AF. Technological improvements and pathophysiological advances have permitted to achieve a safe and efficient management of this arrhythmia, mainly through the development of electroanatomic mapping. Electroanatomic mapping was introduced in the mid-1990's allowing the reconstruction of patient-specific geometry of the cardiac chambers(88), together with the recording of surface electrograms. Image integration of multislice computed tomography or magnetic resonance imaging into mapping system may facilitate catheter positioning, reduce radiation exposure and procedural duration and improve outcomes(89,90).

Various ablation strategies have been described to cure AF (91). The mechanisms sustaining persistent AF are less well understood and its' treatment is still a challenge(92-98). Rotor ablation and substrate-based ablation are probably the two most promising approaches recently described, since they represent a patient-tailored approach aiming its' individual electrical and/or structural sources maintain the arrhythmia (figure 5). Ideally, multi-modality imaging improvements and ongoing-studies should lead to the era of "mechanism-directed therapy" (86). The emergence of the single source theory (rotor) as the possible main driver of AF led clinicians to attempt to map and ablate them(99). Some post-ablation follow-ups have revealed an event-free survival significantly improved in patients treated with focal impulse and rotor modulation (FIRM) as compared to a conventional approach(96,97,100) (101). But, these results have been challenged by short and long-terms clinical results after FIRM ablation that showed poor efficacy. Randomized studies are needed to evaluate the efficacy and clinical utility of this ablation approach for treating AF (102-104) and perhaps, more importantly additive imaging works should improve the understanding and an individualized approach of the therapy.

On the other hand, recent advances have been made in non-invasive mapping of atrial arrhythmias, permitting to detect reentrant activities maintaining AF. Body surface mapping has emerged as a powerful tool to perform a non-invasive bedside mapping to identify AF drivers(105). The system is based on a 252-electrode vest applied to the patient's torso and connected to a system recording unipolar surface potentials (ECVue, CardioInsight Technologies, Cleveland, Ohio)(figure 6)(106). A CT scan is performed prior to the procedure to obtain the patient-specific biatrial geometry and the exact position of each electrode. Unipolar electrograms are mathematically reconstructed during long RR pauses of AF and projected to the biatrial shell. Activation maps of AF are then generated using phase mapping algorithms. AF drivers can be localized, either presenting as focal sources with centrifugal activation or reentrant sources rotating around a central core. Very compelling results were recently published showing that PV regions remain the predominant driver regions in patients with persistent AF, and that the complexity of AF drivers increased with longer AF duration(95,106,107). Indeed, in patients with a persistent AF episode lasting for 12 months or more, extra-PV regions were involved, particularly the inferoposterior LA, the anterior LA/septal region, and the right atrium(106). Procedural AF termination was achieved in 70% of the patients by ablating the driver regions alone, with PV isolation, indicating that such re-entrant and focal activities are the sources maintaining persistent AF(106). This looks like a step forwards for a "mechanism-directed therapy”, but Haissaguerre et al reported that this new technology did not improved the long-term outcome when compared to the standard stepwise approach(95). Further studies are thus, still needed to identify the optimal ablation strategy based on this non-invasive mapping probably combined with anatomical, structural and/ or functional imaging approaches.

Electrical and structural remodeling of the atrium occurs in patients with AF, as demonstrated in animal models of lone AF(108). Clinical studies confirmed that some patients harbor spontaneous atrial scarring, characterized by zones of low voltages(109). Since then, the relationship between atrial fibrosis and electrogram characteristics (fractionation, cycle length, organization, voltage) in patients with persistent AF has been extensively studied. Abnormal myocardium has been defined as bipolar voltage amplitude <0.5 mV and dense scar defined as bipolar voltage amplitude <0.05-0.1 mV(110), although clear definitions are lacking(111), and such values critically depend on the type of catheter and its contact to the atrial surface. A new approach targeting atrial fibrosis was developed by Kottkamp et al, called the “box isolation of fibrotic areas” (BIFA)(112). This concept is based on the assumption of the presence of a specific underlying atrial disease, the “fibrotic atrial cardiomyopathy” (FACM). Four stages of atrial fibrosis were described (from FACM 0, no fibrosis, to FACM 3 with extensive fibrosis), somehow matching the MRI Utah classification(76), although the exact relationship between low voltage areas and late gadolinium enhancement in CMR is still a matter of debate. A detailed electroanatomic mapping of the LA is performed during sinus rhythm at the beginning of the procedure to visualize the extent and localization of low voltage areas (e.g. < 0.5 mV). After performing PVI, a circumferential isolation of substantial fibrotic areas is performed. Thus, for patients with no fibrosis (FACM 0), a PVI-only strategy is performed, a BIFA is added for those with fibrotic zones, while those with extensive fibrosis (FACM 4, the so-called “strawberry atrium") could be denied for ablation due the very low chance of short-term sinus rhythm maintenance. This strategy was proven to show good clinical responses(113). These preliminary results were confirmed by other studies showing a better long-term ablation outcome for those patients with substrate modification following PVI(114). Drivers' ablation (using either the FIRM technology or the non-invasive mapping of AF) and substrate modifications using electroanatomic mapping are promising strategies to perform AF-ablation. These techniques based on pre- or per-procedural imaging and targeting patients' electrical and structural remodeling will allow a "patient-tailored approach" rather than a "phenotype approach" based on the paroxysmal of persistent AF type.

Pre-ablation LGE CMR as a predictor of outcome

LA fibrosis burden quantified by pre-procedural LGE MRI is independently associated with the likelihood of recurrence following AF catheter ablation(76,115). The 4 groups proposed by DECAAF-study(76), are suggesting that LGE CMR might be used to stratify recurrence risk and may help tailor therapeutic strategy. Atrial fibrosis is also associated with the risk of left ventricle systolic dysfunction, development of sinus dysfunction, persistent rather than paroxysmal AF, decreased LA function, LA appendage thrombus formation and subsequent risk of stroke(116).

Impact of post-ablation LGE CMR

LGE CMR could also be useful to characterize radiofrequency-induced scar of pulmonary veins (PVs) and LA. Post-ablation scar appears to be stable by 3 months post-ablation with a degree of enhancement higher than that of fibrotic remodeling on pre-ablation images(117). Residual fibrosis uncovered by ablation scar has been associated with recurrent arrhythmia(118). But, a complete encirclement of all 4 PVs is achieved in only 7% of patients(118), and CMR LGE imaging does not allow to accurately locate PVs reconnection sites in patients having undergone incomplete AF ablation(119). Therefore, again because of a lack of spatial resolution, post-ablation LGE CMR is probably not yet sufficiently reliable to accurately assess PVs and LA scar lesion distribution.

Conclusion

The assessment of LA morphology and function, which has been neglected for a long time, is becoming more and more important in the management of patients with AF. The understanding of the complex interaction between the electrical and anatomical substrates strictly relies upon the combination of different imaging techniques and might contribute to an individualized treatment strategy of AF. Recent advances suggest that LA imaging might also be useful for a tailored preventive treatment of patients at mild-to moderate cardio-embolic risk. Nevertheless, high quality studies remain mandatory for moving from actually used clinical scores to a more image-based individualized approach.

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Figure Legends

Figure 1: Atria and the interatrial septum. Anatomy and orientation

Figure 2: Left atrial appendage exploration and complexity of its anatomy. Value of the 3D-capabilities (A), and cardiac-CT (B)

Figure 3: **Normal LA strain pattern with normal AL reservoir function**

Figure 4: Example of an atrial fibrosis in cMRI.
4A. Axial LGE-CMR image showing delayed enhancement areas of LA posterior wall (arrows) in a patient with persistent AF. 4B. Volume rendering reconstruction showing LGE spatial extent on LA posterior wall in the same patient. (Courtesy Hubert Cochet)

Figure 5: **Illustration of the different imaging approach and different treatments that could be proposed to cure atrial fibrillation by ablative therapies**.

Figure 6: Non-invasive body surface mapping of the left and right atria during AF, in posterior view (ECVue, CardioInsight Technologies, Cleveland, Ohio). A re-entrant activity is rotating counter-clockwise in the posterior LA. Reproduced from Lim HS (106)

Central illustration: How imaging can help for dealing with atrial arrhythmias from the anatomy to the function through the structure of left atrial tissue

Table 1: synthesis of studies performed using LA-strain and looking at atrial fibrillation (AF) or risk of cardiac embolism

	Reference	Methodology	Result
Identification of patients at risk of AF	Hirose T, et al. *(47)*	**Population:** follow-up of 580 patients without documented atrial arrhythmia **Technic to assess atrial function:** velocity vector imaging	Subjects with new-onset AF had lower atrial contractile function: - lower LA active EF (16±5 vs. 28±8%, P =0.001) - lower LA SR at atrial contraction (20.9±0.2 vs. 21.4±0.5 S21, P= 0.001)
	Abhayaratna WP, et al. (120)	**Population:** follow-up of 574 adults without a history or evidence of atrial arrhythmia **Technic to assess atrial function:** volumetric method	Subjects with new AF or atrial flutter had lower LA reservoir function LA emptying fraction (38% vs 49%, p <0.0001)
	Pathan F, et al. (50)	**Population:** 538 Patients with cryptogenic cerebrovascular accidents **Technic to assess atrial function:** 2D speckle tracking echocardiography	Patients who developed AF had lower atrial strain. - Reservoir function: 21.30±7.50 vs. 32.70±8.40 % - Conduit function:11.69±4.80 vs. 17.40 ±6.80 % - Contractile function: 9.60±4.20 vs 15.30 ± 4.40 % (P<0.001 in all)
	Kosmala W, et al. (51)	**Population:** follow-up 146 patients with dual chamber pacemaker implantation **Technic to assess atrial function:** 2D speckle tracking echocardiography	Patients who developed AF had lower atrial strain - Reservoir function: 19.5±9.2 vs 26.1±9.6% (P=0.002) - Conduit function: 10.0±5.2 vs 12.3±6.2 (P=0.04) - Contractile function: 9.4±5.5 vs. 13.8±5.6% (P=0.04)
	Schaaf M, et al. (20)	**Population:** comparison between102 patients without overt heart disease versus 44 patients with paroxysmal AF.	- 3DE: all atrial functions were impaired in the PAF group, regardless of the parameters used (all

		Technic to assess atrial function: 2D and 3D volumetric and speckle tracking echocardiography.	P=0.05) - 2DE: conduit function did not reach significant difference.
	Hubert A, et al (121)	**Population:** 27 male endurance veteran athletes with documented paroxysmal AF vs. 30 control endurance athletes without documented AF **Technic to assess atrial function:** volumetric and 2D speckle tracking echocardiography	Atrial function was decreased in the PAF group Reservoir function: LA ejection fraction: 59.3±12.9 vs 67.6±10.0% (P= 0.01); Strain: 29.3 ± 7.9% vs. 49.1 ± 7.8% (P<0.0001) Conduit function: LA passive emptying fraction: 36.0±16.2 vs 37.9±10.1% (P= 0.591); Strain: 17.0±6.2% vs. 27.0±6.7% (P<0.0001) Contractile function: LA active emptying fraction: 23.4±9.6 vs 29.6±9.0% (P= 0.014); Strain: 12.3±6.4% vs. 22.0±5.6% (P<0.0001)
	Kuppahally SS,et al. (49)	**Population:** 65 patients with paroxysmal (44%) or persistent (56%) AF **Technic to assess atrial function:** 2D speckle tracking echocardiography (velocity vector imaging)	Patients with persistent AF as compared with paroxysmal AF lower midseptal (27±14% versus 38±16%, P=0.01) and midlateral (35±16% versus 45±14% P=0.03) strains. No differences in LA emptying fractions (P=0.07)
Prediction of success of AF reduction	Sarvari SI, et al. (42)	**Population:** follow-up of 61 patients with paroxysmal AF and 20 healthy individuals were included for comparison. **Technic to assess atrial function:** 2D speckle tracking echocardiography (echocardiography performed in sinus rhythm before radio-frequency ablation)	LA mechanical dispersion was more pronounced in patients with recurrence of AF after RFA compared with those without recurrence and controls (38±14ms vs. 30±12 ms vs. 16±8ms, both P=0.001). LA function by strain was reduced in both patients with and without recurrent AF after RFA compared with controls (-14±4% vs. -16 ±3% vs. -19 ±2%, both P<0.05).

	Montserrat S, et al.(52)	**Population:** 33 healthy volunteers and patients with symptomatic drug-refractory AF treated with a first RFCA (n=83) or a second RFCA (n=35) were included. **Technic to assess atrial function:** Speckle tracking echocardiography (echocardiography performed in sinus rhythm before radio-frequency ablation)	LA reservoir function was significantly lower in group treated with a second RFCA as compared to treated with first RFCA or healthy volunteers respectively (30±5, 20±6, 15±5%, P<0.05)
	Montserrat S, et al.(53)	**Population:** 154 patients with AF were treated with RFCA **Technic to assess atrial function:** 3D trans esophageal echocardiography before RFCA.	Patients with recurrent AF had lower atrial function LAEF: 32±15 vs 40±19% (P=0.028) LA expansion index: 48.9 vs 78.9% (P=0.016)
	Habibi M et al (122)	**Population:** 52 patients treated with RFCA and studied for predicting the recurrence by LA function measured with **cardiac magnetic resonance feature-tracking**	LA reservoir function was independently associated with recurrent AF
	Ciuffo L et al (123)	**Population** 208 patients with a history of AF referred for catheter ablation of AF who underwent pre-ablation **cardiac magnetic resonance in sinus rhythm**	Patients with AF recurrence after ablation (n = 101) had significantly higher time to the peak longitudinal strain corrected by the cycle length than those without (3.9% vs. 2.2%; p < 0.001).
Prediction of reverse remodeling after RFCA	Tops L, et al. (124)	**Population:** 148 patients undergoing catheter ablation for AF **Technic to assess atrial function:** strain by tissue Doppler imaging LA reverse remodeling at follow-up: responders were defined as patients who exhibited 15% or more reduction in maximum LA volume at long-term follow-up	At baseline, LA systolic strain was significantly higher in the responders as compared with the non-responders (19±8%vs. 14±6%; P=0.001)
Prediction of stroke:	Obokata M, et al. (54)	**Population:** patients with paroxysmal or persistent AF with acute embolism (82 patients) or without (204 controls). **Technic to assess atrial function:** Volumetric and speckle tracking echocardiography	Atrial function was lower in patients with acute embolism -LA emptying fraction: 20±11 vs 28±13, P<0.001 - Global LA strain : 12.6±3.7 vs 18.9±6.0,

			P<0.001
	Azemi T, et al. (55)	**Population:** Patients with AF, stroke or transie nt ischemic attack and $CHADS_2$ scores ≤ 1 before their events compared with age and gender-matched controls. **Technic to assess atrial function:** velocity vector imaging	Atrial function was reduced in patients compare d with controls - Peak negative LA strain (-3.2±1.2% vs -6.9±4.2%, P<0.001) - Peak positive LA strain (14±11% vs 25±12%, P< 0.001)
	Leung M, et al. (61)	**Population:** follow-up of 1361 patients with first diagnosis of AF for the occurrence of stroke **Technic to assess atrial function:** speckle-tracking echocardiography.	Left atrial reservoir (14.5% vs 18.9%, P=0.005) and conduit strains were reduced (10.5% vs 13.5%, P 0.013), in the stroke compared with non-stroke group.
	Inoue YY et al(125)	**Population** :169 patients, at the time of pre-ablation **cardiac magnetic resonance (tissue-tracking)**	LA reservoir function is significantly reduced and associated with a prior history of stroke/transient ischemic attack in patients with AF
	Ciuffo L et al(126)	cross-sectional study of 246 patients with a history of AF referred for catheter ablation **cardiac magnetic resonance in sinus rhythm**	Higher mechanical dyssynchrony of the LA is associated with a history of stroke in patients with paroxysmal AF.
	Al-issa A et al(127)	18 patients with a prior history of stroke at the time of **CT-scan** and 18 age- and gender-matched controls Four-dimensional motion vector field estimated from CT dynamic images	LAA regional dysfunction is associated with stroke (pilote study)
Prediction of stroke without documented AF	Leong DP et al. (128)	**Population:** 742 patients with cryptogenic stroke and no history of AF, 371 controls **Technic to assess atrial function:** speckle-tracking echocardiography.	LA reservoir strain was significantly lower among patients with cryptogenic stroke (30±7.3% vs 34±6.7%, P<0.001)

Figure 1: atria and the interatrial septum. Anatomy and orientation

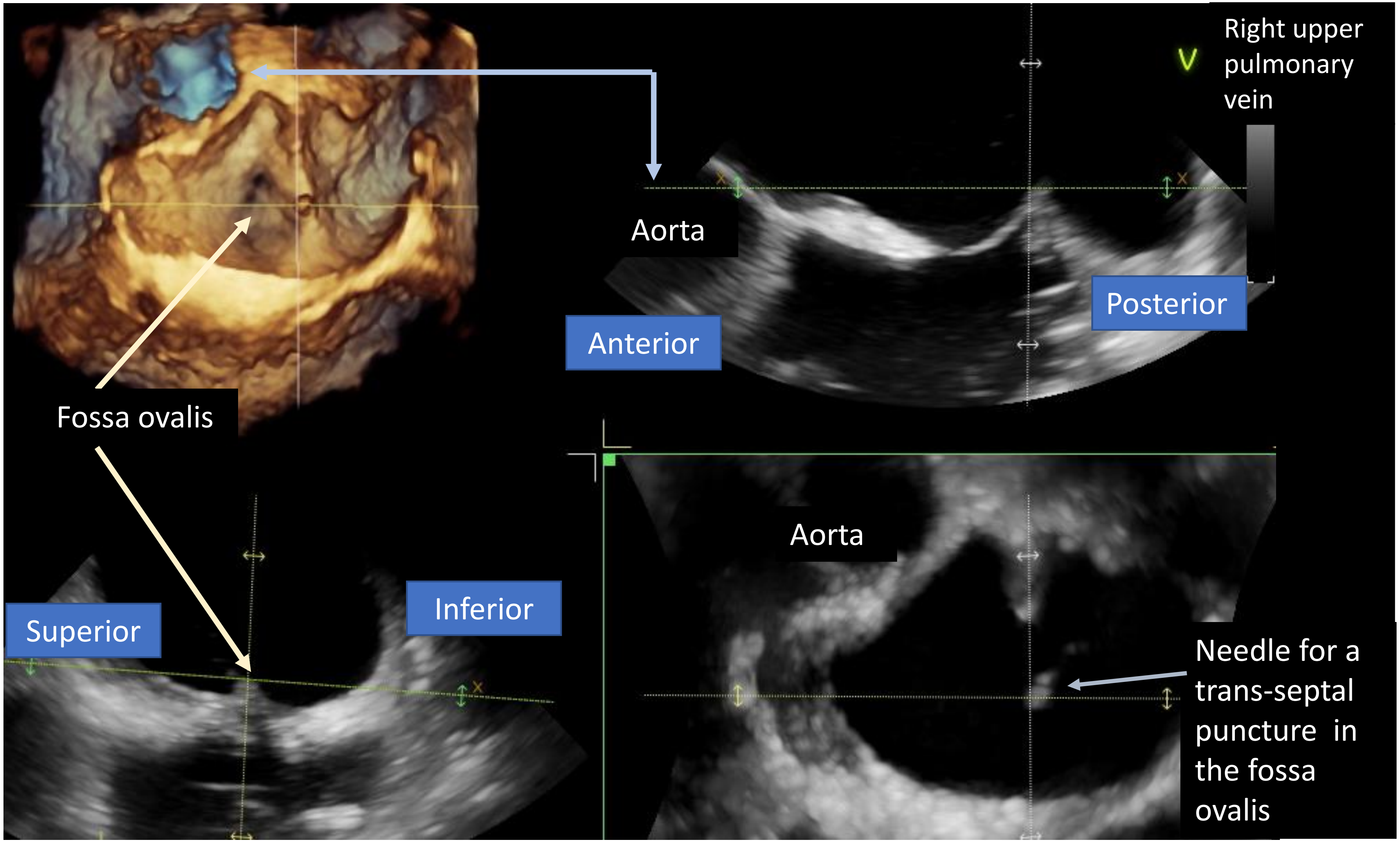


Figure 2: left atrial appendage exploration and complexity of its anatomy that is much better assessed thanks to the 3D-capabilities (A), and cardiac-CT (B)

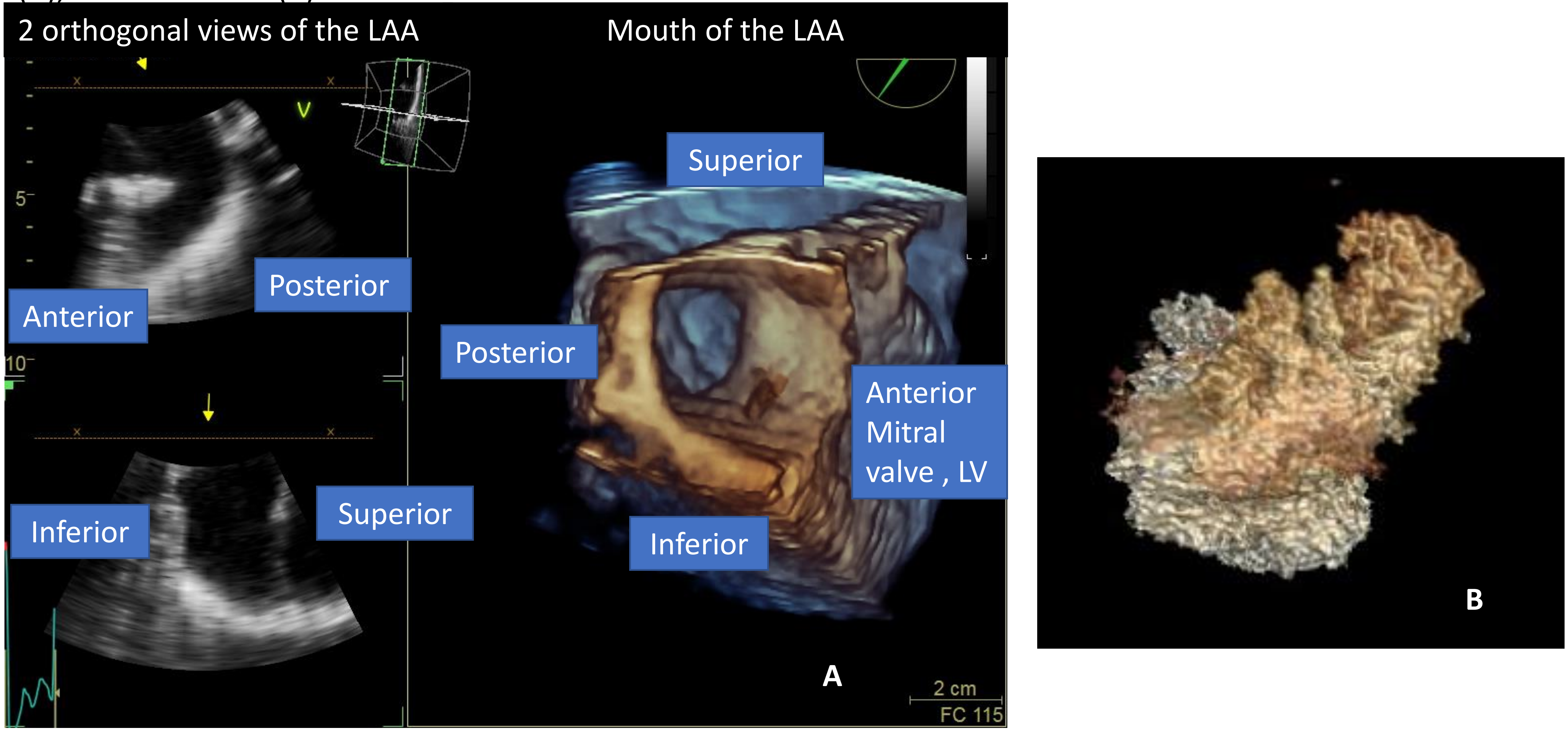
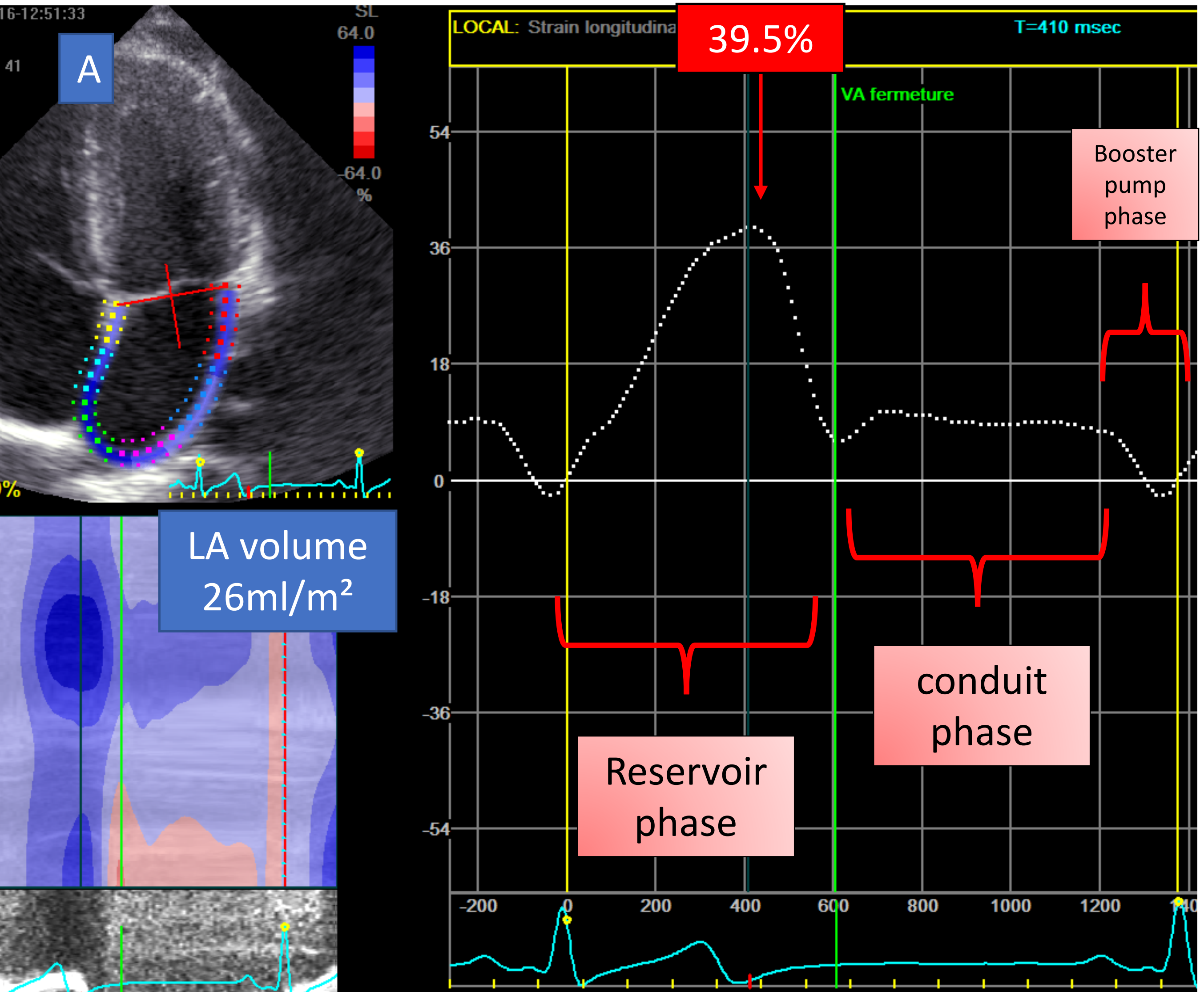
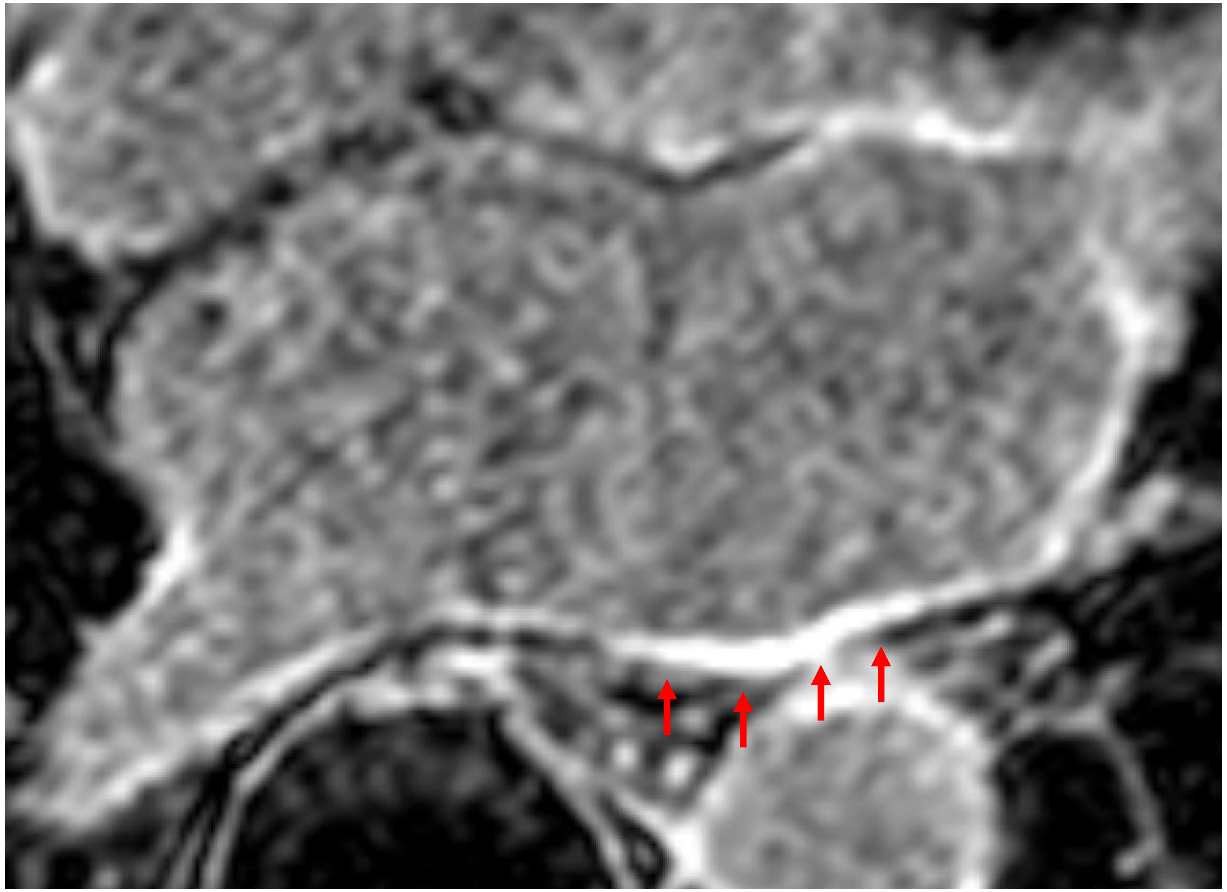


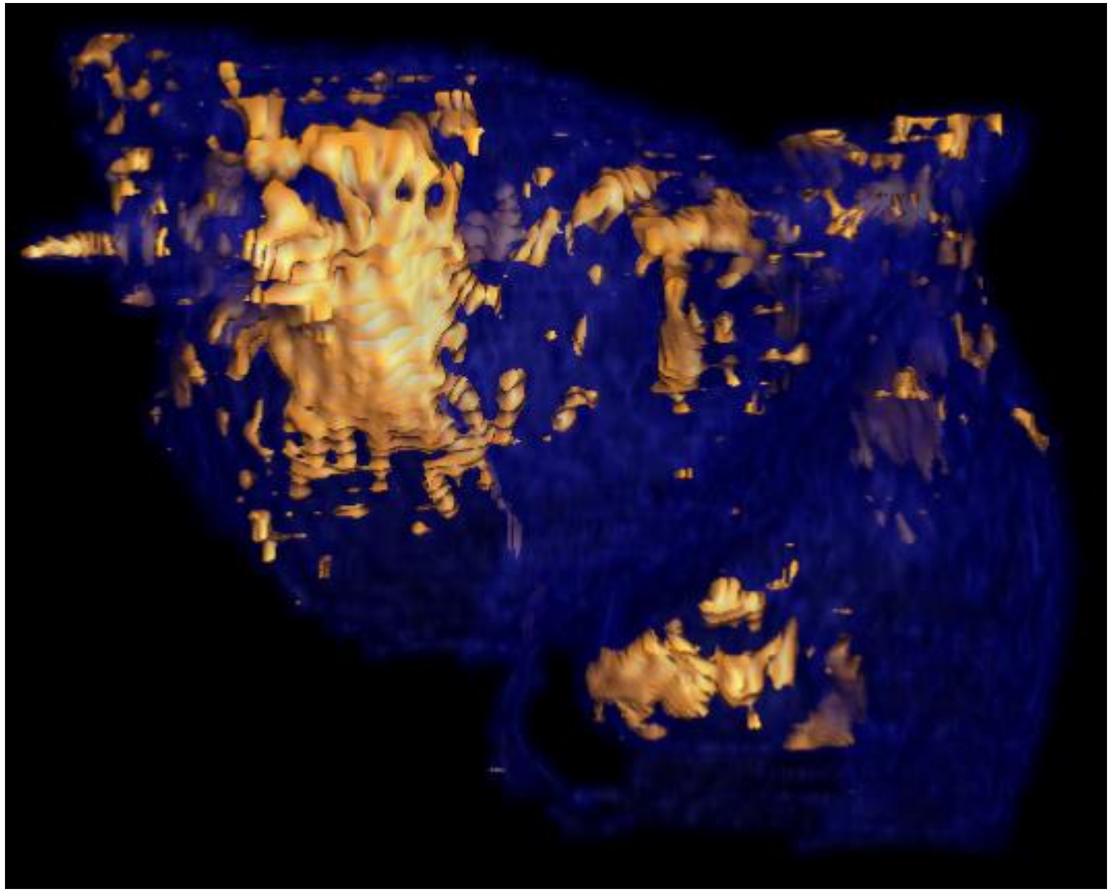
Figure 3: A- normal LA strain pattern with normal AL reservoir function

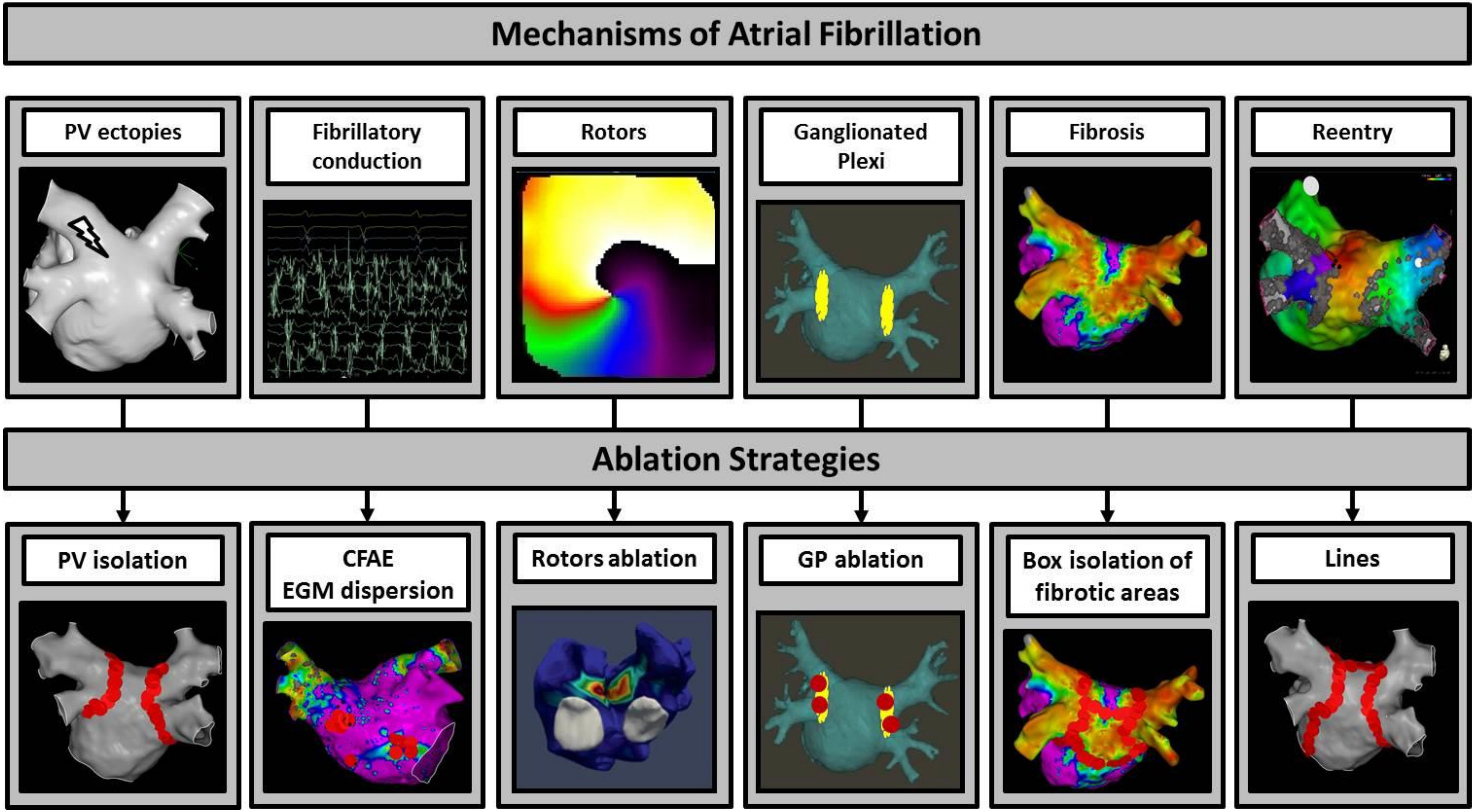


4-A



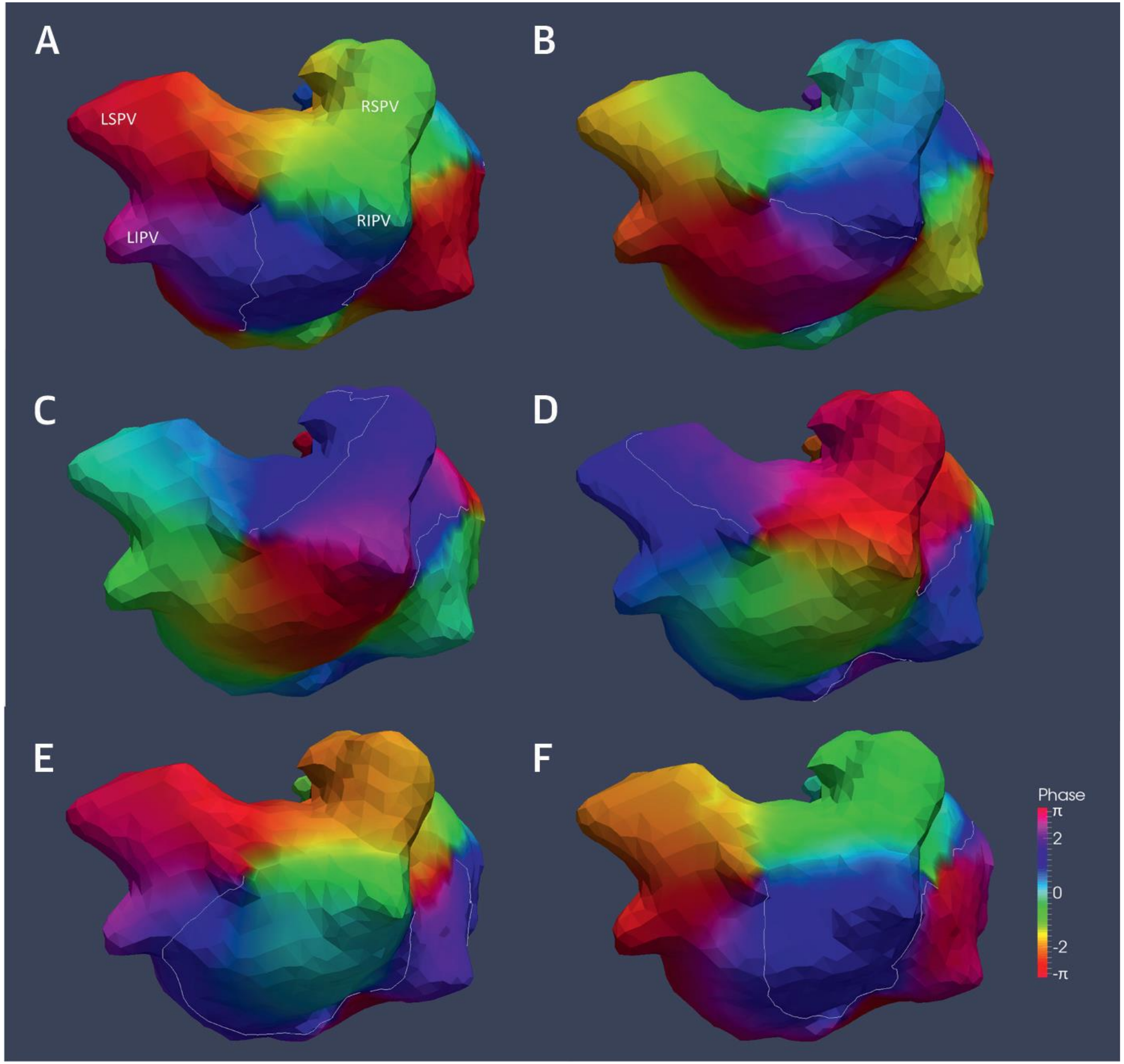
4-B

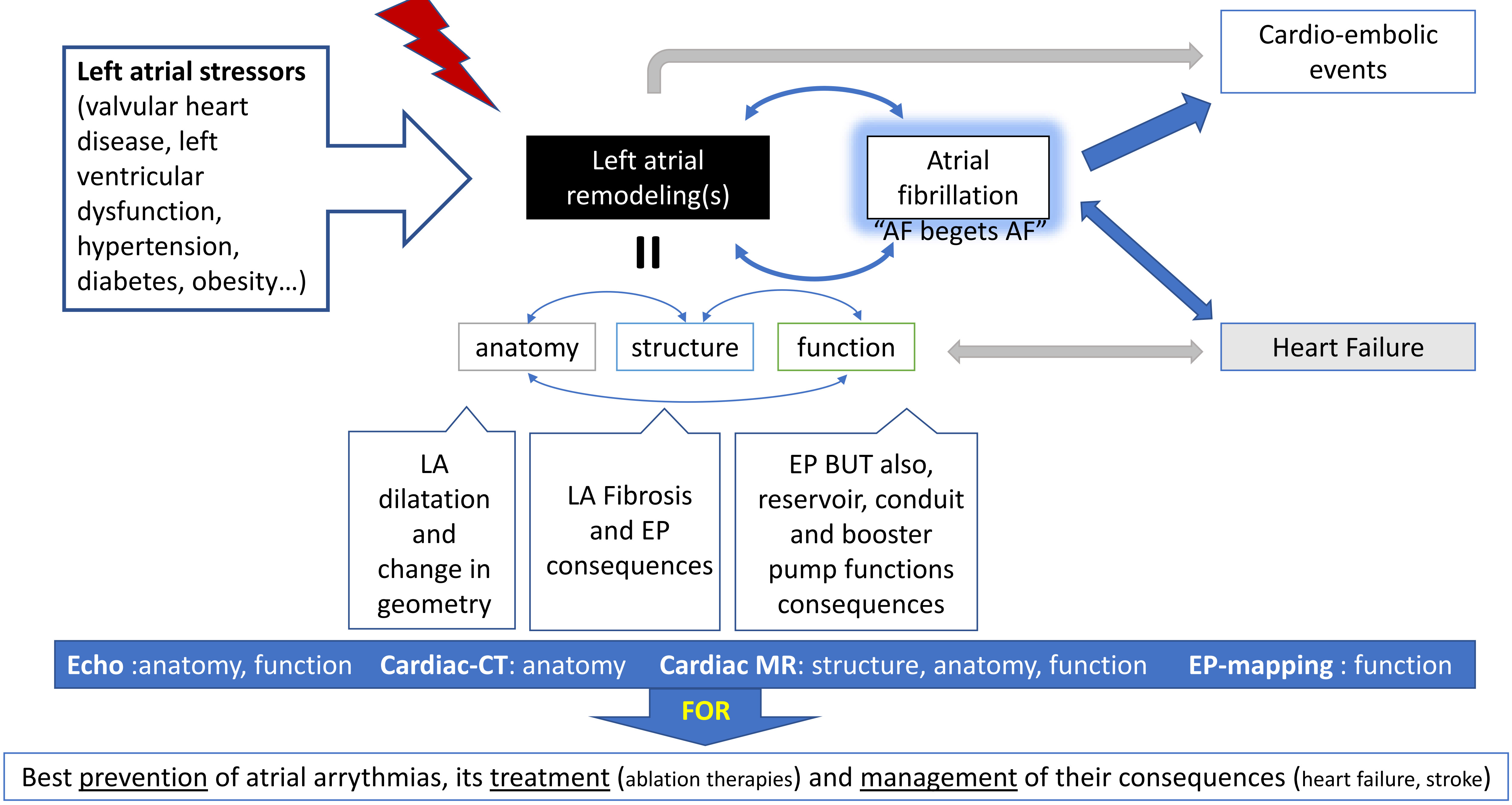




Mechanisms of Atrial Fibrillation
PV ectopies
Fibrillatory conduction
Rotors
Ganglionated Plexi
Fibrosis
Reentry
Ablation Strategies
PV isolation
CFAE EGM dispersion
Rotors ablation
GP ablation
Box isolation of fibrotic areas
Lines

Figure 6: Non-invasive body surface mapping of the left and right atria during AF, in posterior view (ECVue, CardioInsight Technologies, Cleveland, Ohio). A re-entrant activity is rotating counter-clockwise in the posterior LA . Reproduced from Lim HS et al . Lim HS, JACC 2017;69:1257-1269





Central illustration: how imaging can help for dealing with atrial arrhythmias from the anatomy to the function through the structure of left atrial tissue