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The rationale for isolation of the left atrial pulmonary venous component to control atrial fibrillation: a review article

Short title: The left atrial pulmonary venous component

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Abstract:

Catheter ablation of persistent atrial fibrillation is an evolving field. In this review, we discuss the rationale for the isolation of the pulmonary venous component of the left atrium to control atrial fibrillation. The review describes the embryological origin of this component and makes the important distinction between the true posterior wall and the pulmonary venous component, which forms the dome of the left atrium. Studies that have examined the role of left atrial posterior wall isolation in AF ablation have loosely referred to the pulmonary venous component as the posterior wall. We critically re-examine this nomenclature and provide a sound argument underpinned by fundamental anatomical considerations, a clear understanding of which is critical to the operator. Further, we discuss the various techniques employed in isolating this region and review the outcome data of studies targeting this region in AF ablation.

Keywords: persistent atrial fibrillation; catheter ablation; left atrial anatomy; pulmonary venous component; atrial embryology.

Introduction

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder worldwide, with an increased risk of stroke and heart failure.[1] Catheter-based ablation is superior to antiarrhythmic medications with regard to reducing AF-related symptoms.[2] The limited success of pulmonary vein isolation (PVI) in ablating persistent atrial fibrillation has driven the development of a panoply of ablation strategies, including linear lesions, ablation of complex fractionated atrial electrograms, and focal impulse and rotor modulation. Recent trials, however, have cast considerable doubt on the utility of all these approaches.[3,4]

A novel attractive target for adjunctive ablation strategies is the pulmonary venous component of the left atrium. As the left atrium develops, it progressively incorporates the initial common pulmonary vein into its walls until four venous orifices separately enter the roof of the left atrium.[5] The entire pulmonary venous component, therefore, derives from tissue other than the primitive cardiac tube. There is anatomical and electrophysiological evidence that the entirety of the venous component contributes to the genesis and maintenance of atrial fibrillation. Targeting this area of the left atrium

would thus be an extension of pulmonary venous isolation, and a further development of the wide antral isolation, which is superior to ostial pulmonary venous isolation. [6] Catheter-based and surgical ablation approaches to the region of the left atrial wall lying between the orifices of the left and right veins, generally referred to as the left atrial posterior wall in the literature, have shown promise,[7,8] but their feasibility and efficacy have been the subject of controversy.[9,10] As such, the most recent consensus statement on ablation assigns a class IIb recommendation to isolation of the so-called posterior wall.[2]

In this review, we examine the anatomy of the left atrium, paying particular attention to the pulmonary venous component, the fact that it forms the atrial dome, and its relationship to the true posterior wall. We believe that what has been referred to as the posterior wall of the left atrium is in reality the pulmonary venous component and will refer to it as such from this point forward. We then discuss the catheter-based techniques for its isolation, and the current evidence of their efficacy.

Anatomy of the left atrium and its pulmonary venous component

Anatomy of the left atrium

The left atrium is the most posterior cardiac chamber, lying posteriorly and to the left of the right atrium due to the obliquity of the atrial septum. In front of the left atrium lies the transverse pericardial sinus, and anterior to that is the aorta. Its posterior relations are the oblique sinus of the pericardium, which separates the atrium from the tracheal bifurcation and the esophagus. The chamber has muscular walls. It possesses a venous component, which receives the pulmonary veins, along with a vestibule, and an appendage. It shares the septum with the right atrium.[11] All these components are confluent with the atrial body, without clear anatomic demarcations except at the mouth of the atrial appendage. The vestibular component surrounds the mitral orifice. The chamber has been described as having superior, posterior, left lateral, septal (or medial), and anterior walls.[12] We highlight the portion of the fully developed left atrium derived from the original solitary pulmonary vein. Occupying a superior position within the chest cavity, as shown in Figure 1, which is a reconstruction from a computed tomographic dataset, it is well described as the left atrial dome. The myocardial wall separating the two sets of pulmonary veins, however, has previously been ascribed to the left atrial posterior wall.[13] This notion does not stand the test of modern imaging. Viewing the left atrium in an attitudinally appropriate fashion with respect to the chest, it can be seen that the superior pulmonary veins are located anteriorly relative to their inferior partners (Figure 1). Both pairs insert into the superior aspect, or dome, of the left atrial body. The area between the pulmonary veins, therefore, is a superior

component of the left atrial cavity, rather than a posterior one. The true posterior atrial wall runs from the inferior border of the inferior pulmonary veins to the superior margin of the vestibule.

Anatomical and embryological considerations regarding the left atrial pulmonary venous component

The origin of the four pulmonary veins, and the tissue which separates them, can be traced back to mediastinal myocardium derived from a mid-pharyngeal strand at about 6 weeks of embryonic development. The lineage of these tissues is completely different to both the general myocardium of the primary heart tube and the systemic veins. The heart tube initially is attached throughout its length to the pharyngeal mesenchyme by an extensive mesocardium. Only the part of this mesocardium that connects to the body of the atrium survives subsequent to ventricular looping. As the pulmonary vein canalizes within the pharyngeal mesenchyme, it enters the atrial cavity between the persisting reflections. The persisting dorsal mesocardium, therefore, is used as its portal of entry (Figure 2).[5]

The initial solitary opening of the vein into the developing left atrium is through an area that is positive for NKX2.5. This opening, furthermore, is caudal relative to the body of the left atrium. With ongoing development, the

pulmonary veins become incorporated into the atrial body by a process of "cannibalisation". It is this process that produces the atrial dome, initially with a solitary venous orifice to the right and left (Figure 3). With still further cannibalisation, the situation is produced whereby four pulmonary veins drain to the corners of the atrial roof. This migration occurs cranially through and across the area of the true posterior wall. The veins cross the body of the atrium, leaving behind the posterior wall, which is derived from the initial body and vestibule of the left atrium. There is, however, great variability in this process. Only about 75% to 80% of individuals possess four discrete venous orifices.[14]

The only obvious boundary between the pulmonary venous component and the remainder of the left atrium is provided by the fold between the left superior pulmonary vein and the left atrial appendage (Figure 4-A,B). The entirety of the posterior wall is smooth, as is the wall of the pulmonary venous component. Hence, there is no histologic demarcation at the venoatrial junctions. A distinctive border zone, however, can be identified at the junction of the atrial body with the mouth of the appendage, which is similar in histological terms to the walls of the right atrium.[15]

The thickness of the wall of the pulmonary venous component varies considerably, being related to the thickness of the septo-pulmonary bundle.[14] This bundle originates anterior to the interatrial groove posterior to Bachmann's

bundle and passes over the dome, where it can be up to 6.5mm thick. It then descends over the posterior wall in close relation to the right pulmonary venous antrum , the result being that this antrum is thicker than its left counterpart.[14] The atrial wall is thinner in patients with AF and demonstrates a thickness gradient in the sagittal plane, being thinner at the level of the superior pulmonary veins . This area is thus the thinnest of the pulmonary venous component and is associated with a greater risk of perforation and complications of thermal injury during ablation, such as the rare but often lethal atrio-esophageal fistula.[16] Posteriorly, the pulmonary venous component is adjacent to the esophagus, but the true posterior wall is formed by the body of the left atrium and the vestibule (Fig. 4-C,D).

The myocardial architecture in normal pulmonary veins is highly variable. The longest myocardial sleeves are found in the superior veins, being thickest at the venoatrial junction in the left superior pulmonary vein. These sleeves consist mainly of circularly or spirally oriented bundles of myocytes, with additional bundles that are longitudinally or obliquely oriented, with areas of discontinuity measuring several millimetres wide.[15] This complex arrangement, along with other factors, such as stretch and local fibrosis, can promote non-uniform anisotropic conduction, which is thought to play a pivotal role in arrhythmogenesis.[17] Furthermore, in molecular terms, the pulmonary venous myocardial cells share many characteristics with the cardiomyocytes of

the sinus node, displaying higher diastolic calcium levels, and showing a propensity to spontaneous depolarization.[18]

Electrical conduction in the left atrium

Left atrial activation in sinus rhythm

Non-contact mapping has revealed the posteroseptal wall of the left atrium to be the most common site of earliest left atrial endocardial activation. The activation wave front then sweeps across the left atrial dome, being bounded by a line of functional block that extends from the left atrial roof to the interatrial septum just below the fossa ovalis, descending between both pairs of pulmonary veins. This line corresponds to the orientation in the septo-pulmonary bundle. It is variably complete, allowing for potential collision of wave fronts in the pulmonary venous component.[19]

Electrical properties of the pulmonary venous component

The area in-between the right and left pulmonary veins has been found to be a frequent source of triggers, accounting for about 38% of such non-pulmonary vein triggers in one study.[20]

The electrical properties of the myocytes of the pulmonary venous component have a direct bearing on atrial fibrillation. In a swine model, where there is one pulmonary venous orifice on either side,[21] only shortening the effective refractory period of the pulmonary veins and left atrial posterior wall was significantly associated with the inducibility of atrial fibrillation.[22]

Another common electrophysiological property is the response to adenosine. Adenosine has been used to unmask pulmonary vein dormant conduction, restoring conduction in pulmonary veins with incomplete ablation lesions. This depends on a selective action on pulmonary veins, where it hyperpolarizes pulmonary venous myocytes by increasing adenosine-sensitive potassium current (IKAdo), an effect it does not have on atrial myocardium. This can restore excitability by removing voltage-dependent sodium channel inactivation.[23] A similar effect on reconnection of the pulmonary venous component has been clinically observed in one study, with adenosine-induced transient reconnection of the pulmonary venous component reported in 17%, and a comparable pulmonary vein reconnection rate of 11%.[24]

Isolated neurons and even small ganglia have been found between atrial muscle fascicles, including the pulmonary vein sleeves. Five groups of ganglionated plexuses have been described in relation to the atria.[25] The superior left atrial ganglionated plexus is related to the left atrial dome between the pulmonary veins while the superior right atrial ganglionated plexus lies on

the posterior superior surface of the right atrium close to its junction with the superior vena cava, both of which are connected with extracardiac ganglia via cardiopulmonary nerves and to the right and left vagosympathetic trunks by small mediastinal nerves.[26]

These two plexuses are believed to modulate extrinsic cardiac innervation and facilitate the occurrence of atrial fibrillation in a hyperactive autonomic state. Vagosympathetic innervation, which relays in the superior ganglionated plexuses, proceeds afterwards to the neurons in the ligament of Marshall and inferior left ganglionated plexus.[27] It is thus reasonable that lesion sets applied to the pulmonary venous component would greatly attenuate the input of several plexuses to the pulmonary veins as well as interrupt input to the ligament of Marshall. Further, the region of the left atrial appendage adjoining this ligament, where differently orientated cardiomyocytes meet, favours anisotropy. Although there is some evidence in support of isolating the appendage, how much triggers from this structure contribute to the development and maintenance of AF is unclear. [28–30] The benefit from its electrical isolation may well be due to the modification of the surrounding arrhythmogenic substrate, left atrial debulking, or interruption of autonomic input.

Fibrillatory conduction in the pulmonary venous component

The increasing duration of atrial fibrillation is characterized by lower wave conduction velocity and highly complex local activation patterns.[31] The venous component exhibits greater conduction heterogeneity and anisotropy in those with persistent AF than in sinus rhythm. This correlated with fractionated electrograms and remained stable over time.[32] Mapping of fibrillatory waves during cardiac surgery in the presence of persistent AF has revealed the simultaneous propagation of longitudinally dissociated fibrillation waves, which are separated by continuously-changing lines of block. These lines were most densely packed in the pulmonary venous component, leading to the highest degree of block and dissociation, and the lowest percentage of wave front boundaries being formed by collision.[33]

Catheter-based isolation of the pulmonary venous component

Observations during Cox-Maze AF surgery have highlighted the importance of the posterior wall of the left atrium, along with the pulmonary venous component, in patients with persistent fibrillation.[34] Isolation of the pulmonary venous component of the left atrium , including, to variable degrees, the superior segment of the true posterior wall, has been utilised as an adjunct to pulmonary vein isolation (PVI) for catheter ablation for atrial fibrillation.

Various approaches have been described in order to isolate the venous component, each having their advantages and pitfalls (Figure 5).

The first approach to isolating the pulmonary venous component, the so-called 'box' lesion, connects bilateral pulmonary vein-encircling lesions by placing two linear lesions connecting the superior and inferior ends of both lesion sets to one another.[7,24] While this delivers less radiofrequency (RF) energy, gaps or reconnection across either line can lead to its failure.[9,10] The second approach is ablation or debulking of the tissue between both pulmonary vein lesion sets, further extended by some operators to the true posterior wall down to the level of the coronary sinus, with the endpoint of abolishing electrical activity between the veins.[7,35] This technique circumvents the inherent weakness of lines but uses extensive local ablation. The single ring approach aims to isolate the pulmonary veins as well as the venous component by a single ring. Initial attempts had very limited success and were plagued by high rates of reconnection, where reconnection at a single point would compromise the isolation of the veins as well as the venous component altogether.[36,37]

The addition of box isolation to PVI has been shown to reduce the 1-year recurrence rate in persistent AF when compared with PVI plus linear lesions,[8] and was found to be superior to PVI alone in persistent AF during a 3-year follow up.[7] A recent meta-analysis revealed that isolating the venous component did not compromise the pump function of the left atrium, had no significant

increase in the complication rate over PVI alone, and did not prolong fluoroscopy and procedural times significantly.[38] Targeting low voltage areas (< 0.5 mV in sinus rhythm) to guide isolation of the pulmonary venous component might improve atrial arrhythmia-free survival in persistent AF. [39] On the other hand, a study involving 120 patients (only 40% of whom had non-paroxysmal AF) failed to show a benefit from pulmonary venous component isolation.[10] It is possible that a difference would have been more apparent in a cohort of persistent AF patients.

Although typically achieved using radiofrequency energy, a recent retrospective study employing adjunctive pulmonary venous component/posterior wall isolation using the second generation cryoballoon found it to confer a higher 12-month freedom from atrial arrhythmias compared to PVI alone. Notably however, 32% of the venous component isolation group needed additional RF lesions to achieve complete isolation.[40]

Potential disadvantages to isolation of the pulmonary venous component

Atrio-esophageal fistula is a potential risk associated with ablation lesions in close proximity to the esophagus. Although more extensive left atrial ablation would be expected to increase the incidence of fistula formation, there

is no evidence to date of increased risk with pulmonary venous component isolation.

Likewise, injury to the periesophageal vagal branches has been well described in several case reports following left atrial and posterior right atrial ablation.[41]The incidence of this complication following different left atrial ablation strategies has yet to be formally reported.

There is a risk of iatrogenic re-entrant atrial tachycardias after isolating the pulmonary venous component in addition to PVI. The reported incidence of peri-mitral flutter is 7-20%,[10,42] with no significant difference compared with PVI alone.[38]

Another concern while isolating the pulmonary venous component would be a left-sided sinoatrial nodal artery, which exclusively provides blood supply to the sinoatrial node in up to 30% to 40%. Variants of the course of this artery cross the dome in about 47% of such cases, with the potential for a heat sink effect limiting the ability to create effective lesions.[43] Sinoatrial node ischaemia has also been reported with the creation of roof lines.[44] However, its incidence has not been reported to date in prior clinical studies of ablation of the pulmonary venous component.

Hybrid approach

A hybrid approach to AF ablation, involving minimally invasive (thoracoscopic) surgery as well as catheter-based ablation has been described. More commonly, this involves an initial epicardial thoracoscopic procedure to deliver epicardial lesions to the accessible tissue of the posterior wall and the pulmonary venous component up to the level of the oblique sinus, including the ganglionated plexuses residing in the epicardial fat pads. Subsequent catheter-based ablation completes the isolation of the venous component superiorly and anteriorly, and creates a Cavo-tricuspid isthmus line. This approach has a 1-year rate of sinus rhythm maintenance of 56 – 94%.[45,46]

Conclusion

The added value of isolating the pulmonary venous component is plausible from a mechanistic point of view, as well as from the clinical evidence available, albeit limited. This objective will probably become attainable with developments in electro-anatomical signal processing, identification of fibrosis, alternative energy modalities as well as combined endo-epicardial approaches. We view the isolation of the pulmonary venous component as an extension to isolation of the pulmonary veins, and can thus be a significant adjunct to the therapy of persistent atrial fibrillation, for which there is still no accepted standard of care.

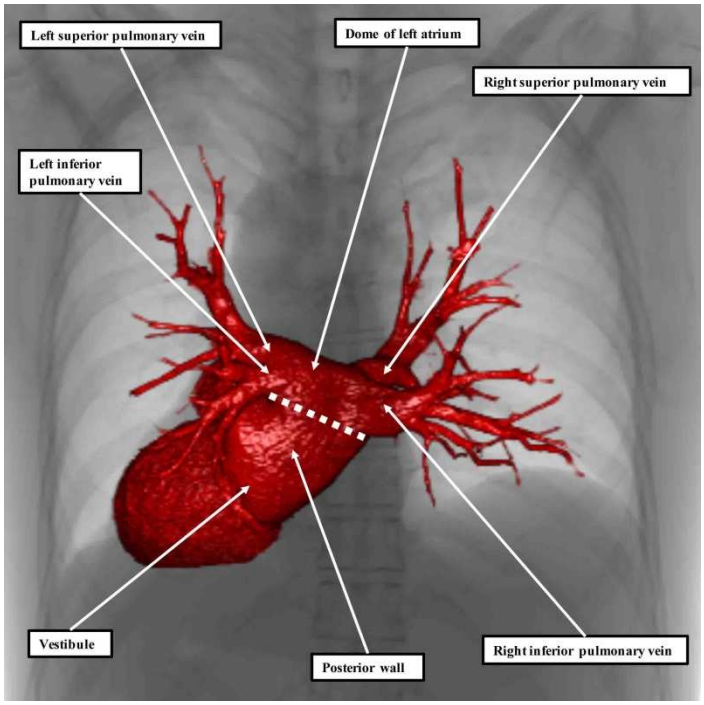

Figure 1; Reconstruction of the left atrium when viewed from behind. The dotted line has been placed at the level of the fold between the appendage and the pulmonary venous component, and extended across to the lower border of the right inferior pulmonary vein. The roof of the pulmonary venous component slopes superiorly from this line, with the dome being positioned superiorly relative to the landmarks of the thorax.

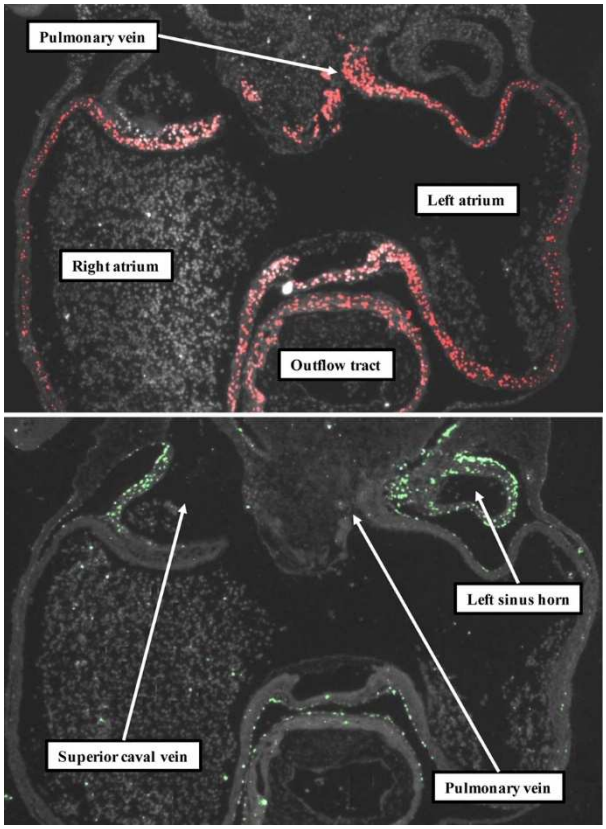

Figure 2*- Sections taken from a human embryo, and incubated with antibodies to, on the one hand, NKX 2.5, which marks the general myocardium, and on the other hand TBX18, which marks the systemic venous myocardium. The sections are taken at the stage when the pulmonary vein has a solitary orifice, entering the body of the left atrium between the reflections of the dorsal mesocardium.* ***The upper panel*** *shows the general myocardium, marked in red, whilst the* ***lower panel*** *shows the systemic venous myocardium, in green. There is no green marker around the orifice of the pulmonary vein. Hence, it is molecularly distinct from the systemic venous sinus.*

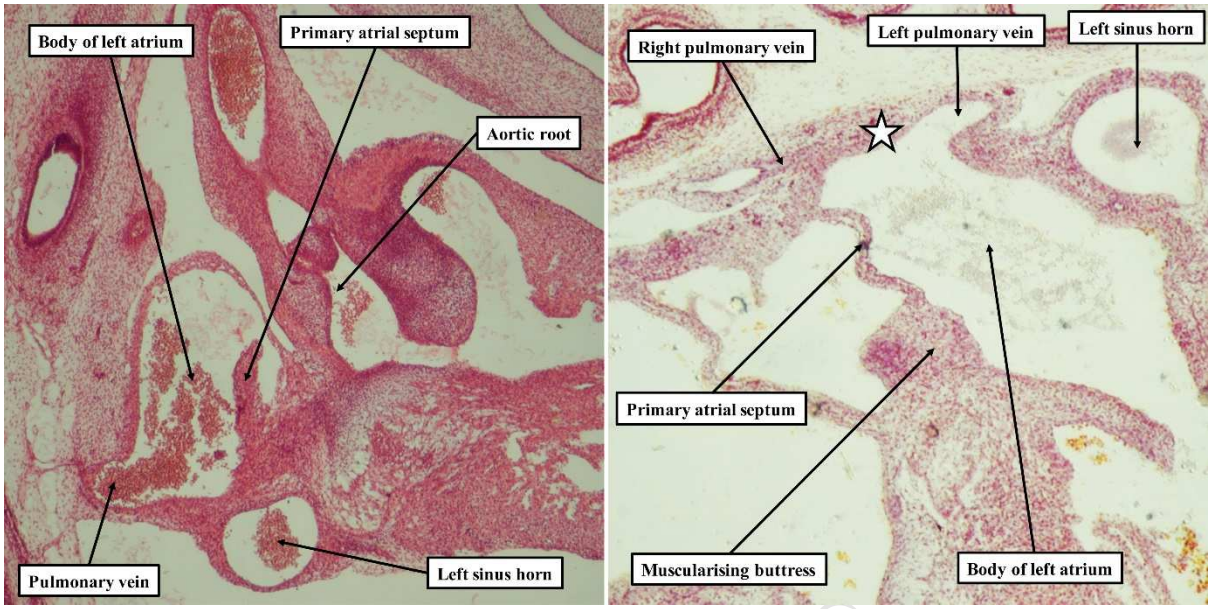

Fig 3- *The image to the left, which is made in the sagittal plane, shows the stage at which the solitary orifice opens adjacent to the developing atrioventricular junction. The image to the right, made in the coronal plane, shows the subsequent stage at which right and left pulmonary veins have migrated to the atria roof. The star shows the developing dome of the atrium.*

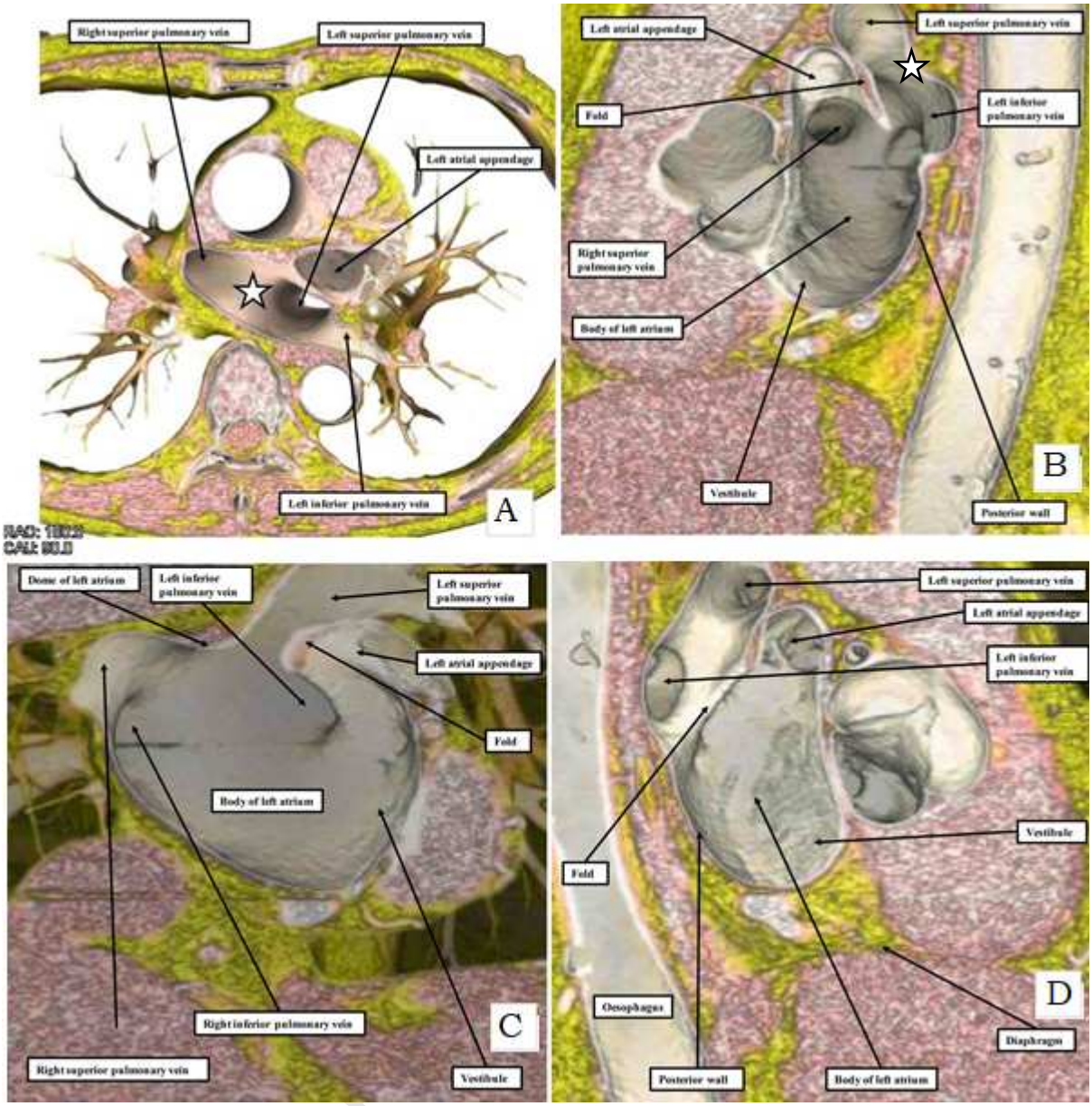

Figure 4*- Transverse (A) and sagittal (B) computed tomographic sections, demonstrating the anatomical relations of the left atrial dome, marked by a star in both images. Coronal (C) and sagittal (D) computed tomographic sections, demonstrating the superior location of the left atrial dome, into which the pulmonary veins enter, relative to the body of the left atrium and the true posterior wall.*

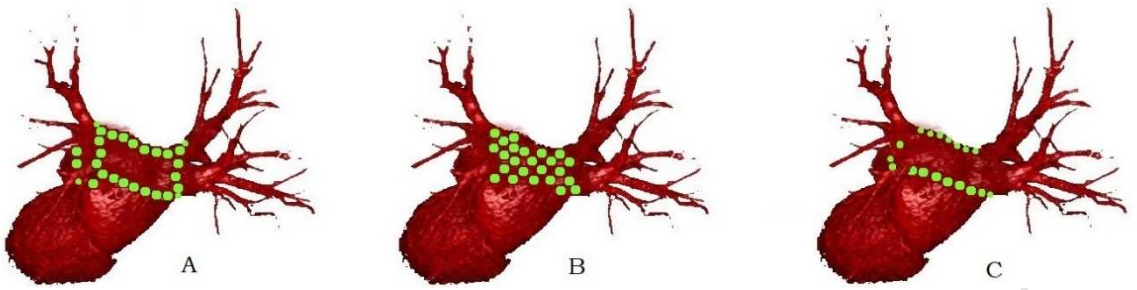

***Figure 5**- Catheter-based ablation approaches to the left atrial pulmonary venous component with ablation lesions (green) applied to a reconstruction of the left atrium viewed from behind. (A) Box isolation of the interpulmonary vein tissue in addition to pulmonary vein isolation. (B)Point by point ablation of the entire venous component. (C) Single ring encompassing the venous component and the pulmonary veins.*

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