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REVIEW

"Form Follows Function": The Developmental Morphology of the Cardiac Atria

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Summary

Although the heart atria have a lesser functional importance than the ventricles, atria play an important role in the pathophysiology of heart failure and supraventricular arrhythmias, particularly atrial fibrillation. In addition, knowledge of atrial morphology recently became more relevant as cardiac electrophysiology and interventional procedures in the atria gained an increasingly significant role in the clinical management of patients with heart disease. The atrial chambers are thin-walled, and several vessels enter at the level of the atria. The left and right atrium have different structures and shape. In general, both atrial chambers have the venous part, the appendage, and the vestibule; different aspects of each part allow us to distinguish morphologically between the left and right atrium. The human atrial conduction system consists of the sinus node and the atrioventricular node with no histologically specialized conduction pathways in the atrial chamber and an interatrial connection. The data show that the propagation of the impulse depends mainly on the myocardial architecture in the atria and the orientation of the myocytes plays a significant role in conduction. To complete the picture, it is also important to know how the atria develop and what is the embryonic origin of its different structures, as this may play a role in the development of some pathological conditions such as atrial fibrillation or certain types of congenital heart defects. Functional impairment of the atria can in some situations severely compromise heart pumping function, and conversely, can support it if other areas are damaged, balancing the blood flow to the body for some time.

Key words

Morphology of atrial chambers • Pectinate muscles • Atrial function

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Introduction

The atria were often overlooked by the researchers because of their lesser functional importance [1] compared to the ventricles. As the number of catheterization and ablation procedures increases, clinicians should be aware of anatomical variations to avoid severe complications during procedures [2]. As some of the cardiac morphologists stress in their work, all description of the human heart should take in consideration its appropriate position to be precise in its description [3,4]. The atrial chambers [5] have thin wall and several vessels are entering at the level of the atria. Left and right atrium (LA and RA) have different structures and shape that allow us to recognize one from the other. The more attention should get not only already known structures but also the structures such as pectinate muscles (*musculi pectinati,* PM) which could eventually have some scientific and clinical importance. From the evidence we already know that the pectinate muscles

show a lot of individual variation in morphology [6] and the human LA is smoother overall than the RA in adulthood, which results from their distinct development [7]. Clinicians focusing on electrophysiology should be aware of the anatomical features of the atria and their variations and potential risks coming from these differences. The aim of this review is to summarize relevant facts about atrial structures, how they develop, and how they are adapted to their function. The concept of "Form follows function", the driving idea of modern American architecture, introduced by Louis Sullivan and Frank Lloyd Wright [8] – obviously applies well also to the achievements of nature's engineering, such as the cardiac atria, as we want to demonstrate bellow.

Gross anatomy

The right atrium

The right atrium is normally located on the right side of the heart, forming the right contour of the heart shadow on the X-ray, and is connected to the right ventricle via the tricuspid valve. The first part is called the venous part where the systemic veins are connected. The superior and inferior vena cava enter the posterior part of the right atrium. The wall of the venosus part is smooth. The second part is termed the right atrial appendage (RAA), or *auricula dextra*, and is larger than the left atrial appendage (LAA) (Fig. 1). These characteristics make it possible to distinguish between the left and right auricle. The RAA is trabeculated (Fig. 1B), dominates the right atrium [5] and is separated from the venous part by the *crista terminalis* or the terminal crest (TC). The part of TC located at the interatrial groove contains a muscular fascicle called the Bachmann's bundle (BB) that extends into the left atrium, which is a part of the conduction system (CS) [5,9]. The atrial trabeculations are known as pectinate muscles, the largest one is called *taenia sagittalis* (TS) [6], which has been described as a single, double, or triple trunk that separates two parts of the RAA – the proximal antral and the distal saccular RAA region [10]. The RAA was divided into five different types: a horse head, a parrot beak, an anvil, a sailboat, and a fifth 'undefined' shape [11]. The atrial wall between the pectinate muscles is thin and transparent [12] with histologically only a few strands of myocytes sandwiched between the epi- and endocardial surface [13] or also described as almost nonexistent in this area [12] presenting a potential risk of perforation during placement of the atrial pacing electrode lead. The TC was described as a natural barrier to the CS [9]. Eustachian valve is the formation between the anterior border of the inferior vena cava orifice [14] and the RAA and during fetal development redirects the blood flow to the patent foramen ovale (PFO), which is one of the fetal shunts. Its form is usually a crescent-shaped fold of endocardium [14]. If the Eustachian valve is enlarged and fenestrated, it is called a Chiari network [5], but it is also absent in about one third of cases [14]. An enlarged Eustachian ridge may create a line of fixed conduction block during typical atrial flutter [14]. The Thebesian valve is a similar structure that separates the coronary sinus from the atrial appendage. The Thebesian valve, which usually covers the coronary sinus, can be present in five shapes – elliptic, semilunar, remnant fold, cord, mesh, and fenestrated – and if enlarged, it can cause a significant obstacle to coronary sinus cannulation [14]. The ostium of the coronary sinus is usually located between the inferior vena cava and the tricuspid valve. In case of an enlarged coronary sinus, there is an increased risk of the atrioventricular nodal re-entrant tachycardia (AVNRT) [15]. The place where the Thebesian and Eustachian valves meet posteriorly is known as the fibrous tendon of Todaro [3]. It forms an apex of the Koch's triangle and can only be identified microscopically [15]. Koch's triangle is a very important region because it contains the atrioventricular (AV) node, which is located in its apex. For this reason, it is not advised to do ablation of the paraseptal isthmus, the base of Koch's triangle, as it could potentially damage the AV node and lead to complete conduction block; however, the Koch's triangle plays a role in the pathophysiology of AVNRT [15]. The orifice of the superior vena cava has no anatomical obstacle [15]. The left atrium is separated by the interatrial septum. The cavotricuspid isthmus is the place between the inferior vena cava and the ostium of the tricuspid valve. The isthmus is a place for ablation in patients with typical atrial flutter which is the isthmus-dependent variant and is the most prevalent in the population [15].

The left atrium

The left atrium has the same features we can find in the right atrium – i.e., the venosus part, the vestibule, and the atrial appendage (Fig. 1). The venosus part of the left atrium is also smooth-walled and contains, in a normal heart, the orifices of four pulmonary veins (PVs). These PVs can vary in their number and arrangements. If we talk about anatomy in the heart, where everything is anatomically correct, we can find two PVs entering on the right side and two entering on the left

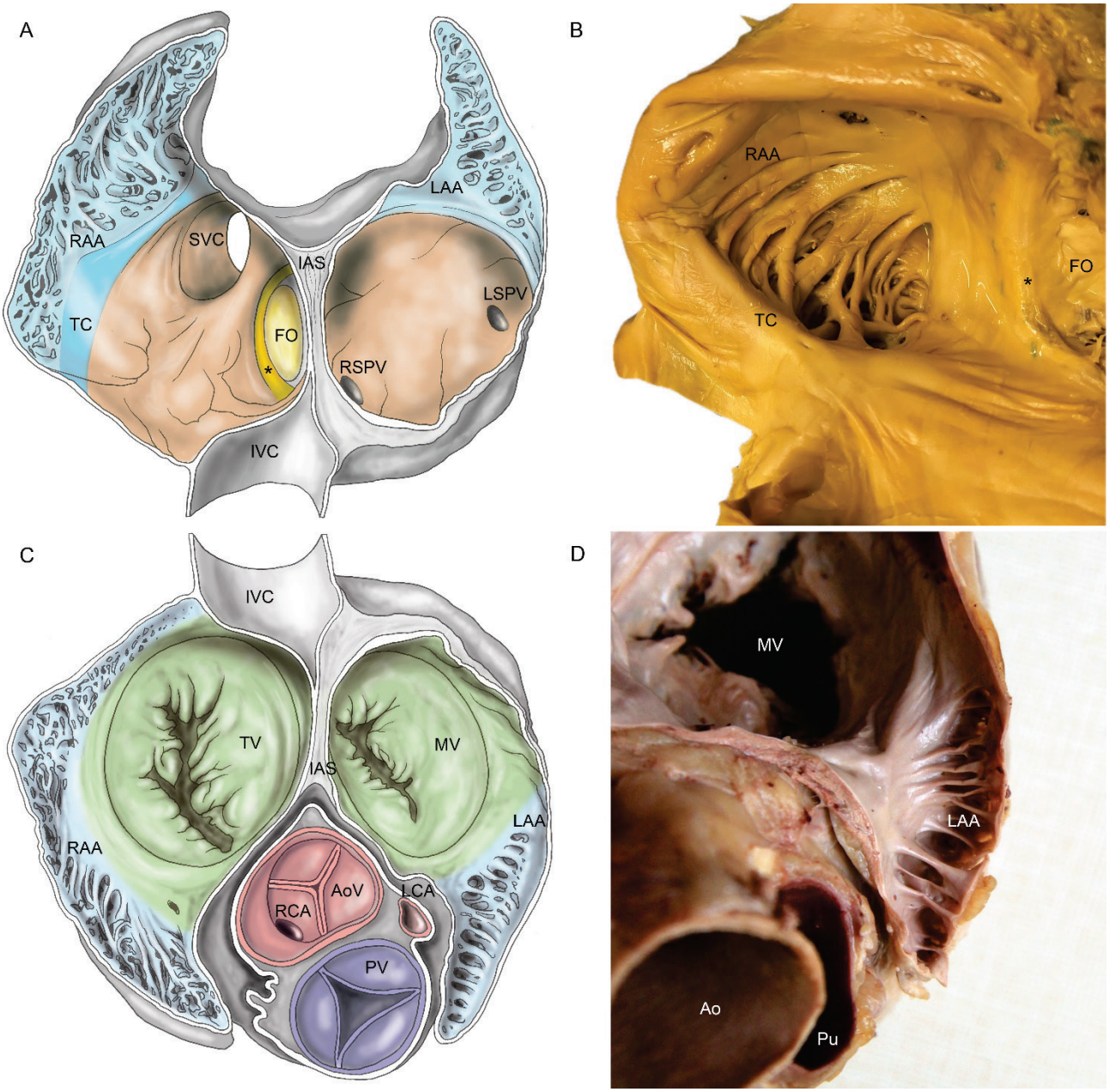

Fig. 1. Morphological overview and anatomical preparations of the human atria. (**A**) view of the roof of the atria and (**B**) view of the RAA and interatrial septum, (**C**) view of the vestibule and (**D**) view of great arteries, mitral ostium and LAA. Ao = aorta, AoV = aortic valve, FO = fossa ovalis, IAS = interatrial septum, IVC = inferior vena cava, LAA = left atrial appendage, LCA = left coronary artery, LSPV = left superior pulmonary vein, MV = mitral valve, Pu = pulmonary artery, PV = pulmonary valve, RAA = right atrial appendage, RCA = right coronary artery, RSPV = right superior pulmonary vein, SVC = superior vena cava, TV = tricuspid valve, TC = terminal crest, * = limbus of fossa ovalis, light blue = appendage, green = vestibule, brown = venous part, yellow = interatrial septum, red = aorta, dark blue = pulmonary artery.

side. The left ones are located more superiorly than the right ones [16]. Patients with chronic atrial fibrillation (AF) have superior PVs larger than the inferior ones and the right ones larger than the left PVs [17]. In the congenitally malformed heart, we can find numerous variations such as a total anomalous pulmonary venous connection, where all the PVs do not enter into the left atrium directly, but the drainage ends in the right atrium, e.g., *via* a vertical vein that enters the superior vena cava or a partially anomalous pulmonary veins connection where one or more pulmonary veins do not enter in the left atrium. We can sometimes find an accessory pulmonary vein from the right or left lung [18]. The thickness of the left posterior atrial wall is not uniform [13]. The vestibule of the morphologically left atrium contains a mitral valve that normally opens into the left

ventricle (Fig. 1D). The LAA is smaller than the right one, its ostium is smaller and contains muscle bundles in all areas. The wall in between the PM is paper-thin [13] which should always be taken into account when ablating near the LAA orifice [16]. The site separating the left PV and the LAA orifices is called the left lateral ridge [13], also known as the Coumadin ridge [23], and described by Keith in 1907 as the left taenia terminalis [16]. Some of the researchers try to look deeper and evaluate the shape of the LAA and they tend to differentiate between four shapes [19] such as cauliflower, chicken wing, cactus, and windsock [20] and they also correlate these morphology types with their role in and a relative risk of thromboembolic events in patients with AF [16,20]. As the incidence of AF is increasing worldwide over the years [21], several studies have been performed in patients with AF and there is evidence of a different anatomy than in patients without AF. Several studies found that patients with chronic AF have anatomic remodeling of all LA structures such as dilation, stretching and reduction of PM volume, which correspond to increased LA volume, PVs ostia and LA appendage, and thickening of the LAA with the appearance of endocardial fibroelastosis, in contrast to patients with paroxysmal AF [17]. The atrial wall thickness is not uniform in the LA and in patients with AF is smaller in the middle and between the inferior venous orifices in comparison to those without AF [22]. The shape of the LAA is important in patients with AF, as the studies have shown that the more complex it is, the higher risk of thrombus formation [20]. The other important factor for thromboembolic events is also the diameter of the LAA ostium, where a wider LAA ostium is prone to systemic embolization during AF [20]. In another study, the authors focused on comparing the mitral isthmus and the LAA isthmus as a new potential ablation site. The mitral isthmus is located between the left inferior PV orifice and the mitral annulus and the LAA isthmus line are located between the LAA orifice and the mitral annulus. In this study, the first of these was found to be longer and more structured than the second one in all cases, which could lead to problems with entrapping of the ablation catheter. These structures are remnants of the PM extending from the LAA [23]. The LAA isthmus line is always shorter and the LAA isthmus is almost in every case smooth [23].

The interatrial septum

The interatrial septum separates the right atrium from the left atrium. It consists of several parts. The inferior part is considered as the main component of the interatrial septum and is composed of the oval fossa (*fossa ovalis)* and its muscular rim (Fig. 1). The superior, antero-superior, and posterior portions are not considered as components of the true septum because they are formed by the infolded wall of the atrial roof between the superior caval vein and the right PVs [13,24] and cannot be excised without perforating the external wall of the heart [15]. The groove that can be seen from the outside of the heart in this place is known as Waterson's groove, and together with the epicardial fat it also usually contains the artery that supplies the sinus (SA) node [15]. We can observe different types of anatomy of the atrial septum – smooth, PFO and different types of atrial septal pouch. The PFO is one of the most common pathologies present in up to 25 % of adults [25]; however, diagnostic tools are limited as it is not often seen in adults on transthoracic echocardiography unless an ultrasonographic contrast agent (glucose mixed with air bubbles) is used. Alternatively, transesophageal echocardiography can be used to diagnose PFO. In addition, there is a difference in incidence between young adults and the elderly people, showing a tendency for its continued obliteration with age [26]. The third type of anatomical variation of the atrial septum is the atrial septal pouch, which was first described in 2006 as a cavity within the interatrial septum [27] or, by definition, incomplete fusion of the septum primum and secundum when the PFO is absent [28]. Holda *et al.* performed a study to clarify the variations of the atrial septum and found left-sided, right-sided, and double septal pouch with higher prevalence in elderly people compared to the PFO in young adults [29]. The clinical relevance has not yet been studied in depth, but the data suggest that this anatomical variation should be considered in patients with cryptogenic stroke as the left-sided septal pouch increases the risk of blood stasis and thrombus formation. Another recent study also showed an association between left-sided septal pouch and the risk of atrial fibrillation and cerebrovascular events [30].

The atrial myoarchitecture

Atrial myocytes are smaller comparing to the ventricular ones, have a shorter action potential duration and contain more of a fetal type of myosin and also atrial natriuretic peptide granules [31]. Two types of myocytes can be distinguished: working and conducting myocytes; the latter ones are not always clearly differentiated in the

atrial chambers. The muscular sleeves found around the pulmonary veins normally contain bundles that are mostly oriented in a circular, oblique, or longitudinal way [16]. These muscular sleeves are supposed to contain specialized conducting myocytes described by Mönckeberg and Aschoff in 1910 [3]. The so-called venoatrial junction, the site between the LA and the PVs, is normally smooth without folds [16]. Many researchers have previously described the possible focal activity in the muscular sleeves around the PVs [32] and caval veins [33] which can trigger the atrial arrhythmias by premature ectopic beats [15]. Myocytes crossing the Marshall vein can connect the Coumadin ridge with the free wall of the LA, the muscular sleeve of the coronary sinus, venoatrial junctions of PVs, and the pulmonary sleeves. This area is a recognized AF trigger point – a source of ectopic activity that initiates fibrillatory activity throughout the atria [16,34]. The arrangement of the myocytes, and thus the myofibers, plays a role in conducting the signal throughout the chambers [5]. As we have already established that the atrial chambers have different thicknesses of different parts of the wall, there has also been shown a connection between the arrangement of the myocytes and preferential pathways. We can see that in the thickened parts of the wall, such as TC or BB, the myocytes are parallel and, therefore, the propagation of the electrical impulse is faster than in the other parts where the myocytes are more irregularly aligned [3]. Generally speaking, the myocytes are aligned parallel to the atrioventricular grooves in the vestibule, but transversely across the atrial roof [3].

Pectinate muscles in the atria

The PM play a specific role in atrial conduction and are therefore as important to the electrophysiologists as the TC. The most important types are those with more complex fibers, as they are more susceptible to be damaged during procedures. There is a risk of the catheter getting stuck between the PM or of atrial perforation [2].

Morphology of the PM

The PM are the luminal trabeculations of the atria. They can be found in the RAA, where they extend from the TC like the *teeth of a comb* [35] as well as in the LAA (Fig. 1). These structures allow us to morphologically distinguish the left and right atria [1] and their morphology also shows a lot of individual variation [6]. PM may help to improve atrial contractility and also prevent excessive dilation of otherwise thin-walled atrial chambers (unpublished data). The PM have some characteristics such as automaticity and contractility. They can also develop a uniform and much larger amplitude of contraction which shows a great potential for experimental evaluation of the effect of inotropic and chronotropic agents [36].

Development of the PM

Atrial trabeculations start to form at 5 weeks (Carnegie stage 16) in humans, at the 12th day of gestation in mouse, and at 5th incubation day (Hamburger and Hamilton stage 27) in chick [1]. During human development, PM start to form first in the right atrium [4]. The left atrial wall in the embryo is smoother than the right atrial wall, which persists into adulthood [37]. Although in ventricles there is less right than left ventricular myocardium, in the atria, there is consistently less left than right atrial myocardium [7]. This could suggest that the reservoir function of the LA is more important than that of a contractile chamber and that the left ventricle works better as a suction pump comparing to the right ventricle. Recently, it has been demonstrated in zebrafish model that the cellular and molecular mechanisms playing role in formation of atrial muscles structures are different from the ventricular ones [38].

Patterns of the PM

The pattern of PM, which roughens the luminal surface, is similar to the veins of a leaf, but there can be significant differences between species [1]. Siddiqui *et al.* [2] proposed 6 types of patterns of pectinate muscles and 3 types of TS. In the RAA, PM could be found in an arrangement perpendicular (type 1) or parallel (type 2) to the TC, or a combination of both (type 3). The other types found are described as the branching (type 4), interlacing trabeculations (type 5), and prominent muscular columns (type 6) of pectinate muscles. TS was either absent (type A) or seen as a single (type B) or multiple trunk (type C) [2].

Surface area of PM

Several researchers paid attention to different attributes in the LAA in patients with AF. Peterson in 1987 observed the LA in patients with chronic AF during echocardiographic examination. Ernst in 1995 compared the casts of the LA of patients with AF and those with sinus rhythm [39]. Shirani and Alaeddini focused on the LAA during the necropsy of the hearts of patients with

and without chronic AF [40]. These experiments concluded that the volume of the LAA is increased in patients with AF compared to those in the sinus rhythm; finally, those with chronic AF had a greater volume of the LAA than those with paroxysmal AF. Shirani and Alaeddini also examined the surface area of the transected PM in these hearts. They found that the PM occupied 7 to 85 % of the total LAA surface area and nearly ¾ of patients with chronic AF had endocardial fibroelastosis in the LAA, which resulted in a smoother LAA luminal surface and encased the pectinate muscles (embedded in the thickened fibrotic endocardium) and decreased the PM percentage of the total LAA surface [40].

Our area of interest in the atrial chambers are also PM which have not yet received enough attention, compared to the *trabeculae carnae* in the ventricles. We were interested in the relative mass of the PM during development in reptiles available in our lab. As a proxy, we performed a study of the relative surface area of the PM on histological sections [41] of Siamese crocodile, Corn snake, Central bearded dragon, and Leopard gecko (Fig. 2). We measured the total surface area of the PM in the RA and LA during different stages of embryogenesis (Fig. 3) and expressed it as a percentage of the total atrial myocardial cross-sectional area. In the hearts of the latter two, the surface area of the PM occupied similarly around 20-45 % of the total surface of the RA and the LA. The PM in the heart of Corn snake occupied 40-56 % of the total volume of both atria. The most variable results were found in the hearts of Siamese crocodile where the surface of the PM varied from 21 to 71 % in the RA and from 28 % to 61 % in the LA. While in general the smaller hearts have a more extensive PM network [1] than the larger ones, these results suggest that other factors may be at play, at least in the reptiles.

Atrial conduction system

The atrial conduction system consists of the SA node, AV node, internodal tracts, and interatrial connections. The criteria established Mönckeberg and Aschoff for conducting tract cells are not applicable to atrial conduction cells, as both the SA and AV nodes do not fulfill the criteria [42,43]. Anatomic substrates for normal and abnormal conduction can be found in the atria [44].

SA node

The sinus node was discovered by Keith and Flack in 1907 and is described as a crescent-shaped [15] or spindle-shaped structure [44]. Its morphology is simpler than that of the AV node and is located in the superior cavoatrial junction [15]. Its function is known as the physiological pacemaker of the heart [15] and it serves to activate the atrial myocardium. The SA node

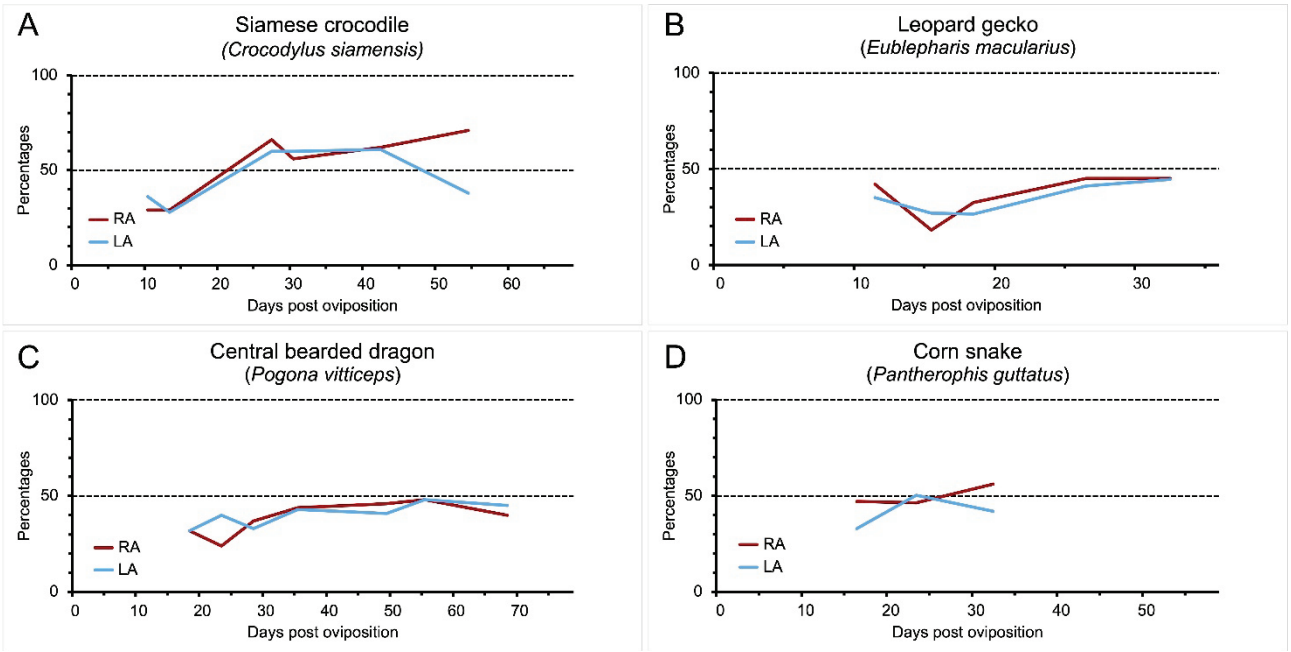

Fig. 2. Graphs showing the proportion of cross-sectional surface area of PM during embryonic development of (**A**) Siamese crocodile (*Crocodylus siamensis*), (**B**) Leopard gecko (*Eublepharis macularius*), (**C**) Central bearded dragon (*Pogona vitticeps*), (**D**) Corn snake (*Pantherophis guttatus*). Note that in all species, the PM form about 50 % of the atrial muscle in both atria. RA = Right atrium, LA = left atrium.

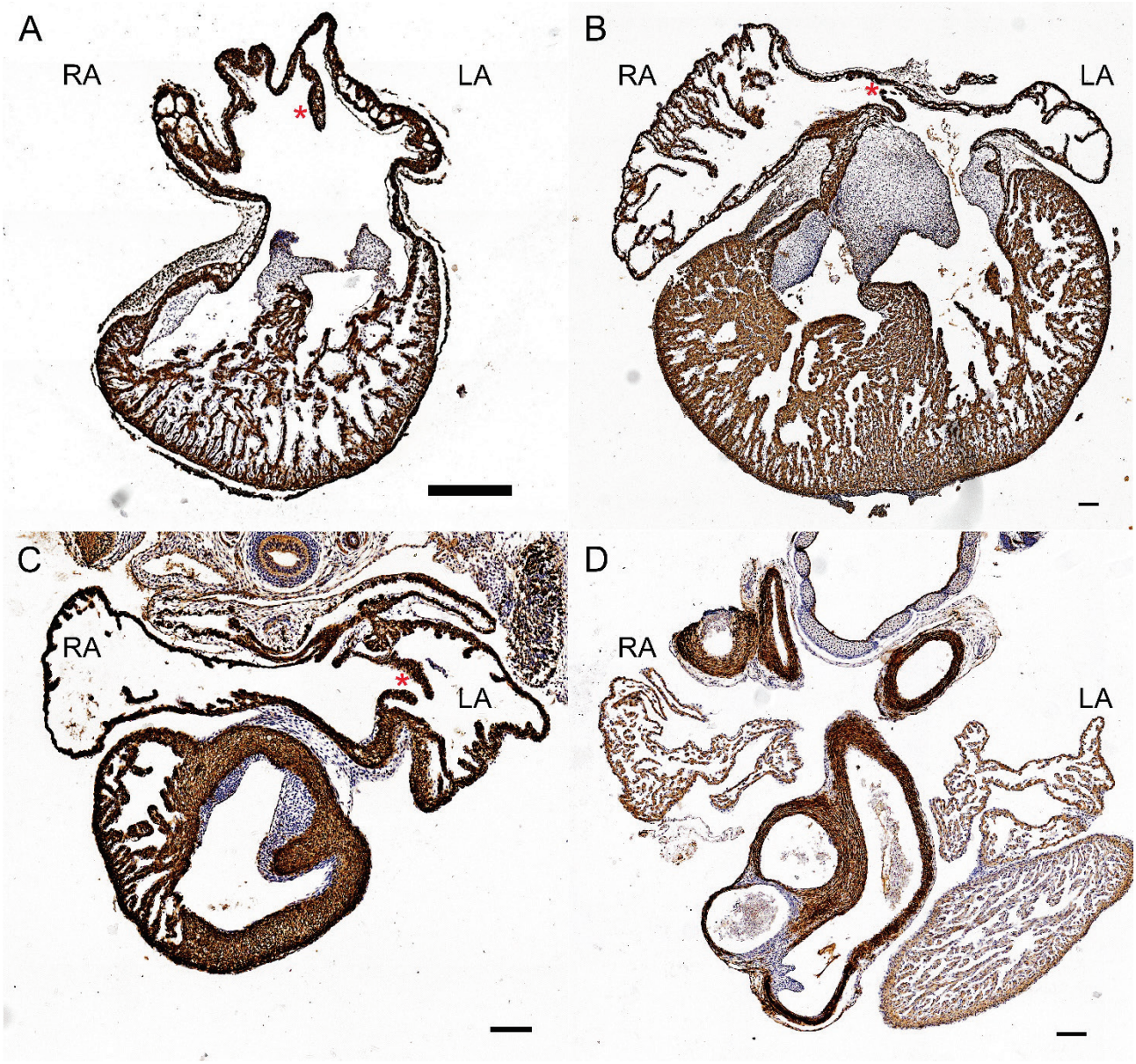

Fig. 3. Histological sections of non-model reptilian species during different stages of embryogenesis. Immunohistochemical staining with anti-smooth muscle actin antibody [41]. Siamese crocodile (**A**) 13 and (**B**) 27 days post oviposition and Central bearded dragon (**C**) 28 and (**D**) 55 days post oviposition; RA = right atrium, LA = left atrium, * = interatrial septum, scale bar corresponds to 100 μm.

contains histologically specialized cells that are not insulated from the working atrial myocardium with a small zone of interposing cells [44]. The transitional cells are limited to short tongues that interdigitate with musculature of the TC [44]. The transitional cells have ultrastructural features of Purkinje cells but also some of those of regular working myocardial cells [45].

AV node

The AV node was first described in the study of Tawara in 1906. It is a compact node with characteristic histologic appearance – half oval of distinctive interweaving cells, in the direction to the atria, it often bifurcates [44]. It is located in the apex of the Koch's triangle [13]. It is not insulated from the working atrial myocardium [44] and it is surrounded by an area of transitional cardiomyocytes [15]. The node itself occupies a smaller area than the transitional cells around it. There are no precise morphologic criteria for these transitional cells, but their arrangement was described as a circumferential cap [44]. The transitional cells entering the Koch's triangle and joining the node superiorly, inferiorly, posteriorly, and from the left [44]. The distal extension of the AV node is distinguished by the presence of a fibrous

collar surrounding the specialized cells [44].

Internodal and interatrial connection

Electrical activity spreads radially in the atria [45]. The impulse seems to spread more or less in concentric isochronal lines with a suggestion of a more rapid propagation along the BB and a preferential pathway around the taenia terminalis [46]. The BB is a fundamental connection of the RA and the LA for spreading the impulse from the SA node [47]. The atrial myocardium, unlike the ventricular bundle branches, does not contain any insulated or discrete conducting pathways [44]. As already mentioned previously, it seems that the propagation of the signal is depending on the orientation of the myocytes and fibers. Evidence shows that PM contain fibers in the parallel orientation which favors preferential conduction. The orientation of the fibers can also present morphological substrate for reentry and AF which is caused by heterogeneities in fiber orientation [1]. There are no insulating fibrous sheaths around muscular bundles, the supposed atrial tracts merge with the atrial myocardium [44]. The transitional cells found around the nodes interpose between the working atrial myocardium and the unequivocally specialized compact AV and SA nodes [44]. We cannot distinguish histologically between the AV node and the proximal penetrating bundle. The bundle entering the fibrous body shows an insulating collar, therefore, no atrial events can influence the conduction [44]. Cells proximal to the central fibrous body can function as inputs into the conduction axis [44]. There is evidence that some internodal tracts are present [48]. We can distinguish three tracts connecting the SA and AV nodes – the anterior, the middle and the posterior tract. There is still a lot of controversy about these tracts, because there are no strictly specialized pathways that would be formed exclusively by Purkinje fibers, as in the ventricles, but there are tracts mixed with fibers of the working myocardium [45]. The anterior and middle one come to the crest of AV node while intermingling when approaching AV node and the posterior tract contains so-called bypass fibers as this tract passes along the convex right atrial surface of the AV node and enters its lower position. In all tracts, Purkinje fibers are found with ordinary myocardial fibers, and all three tracts communicate [45]. Cells shorter and broader than working myocardium are found in the BB and the Eustachian ridge and possess the cytologic characteristics of Purkinje fibers [45].

The most important milestones during vertebrate cardiovascular evolution

The heart differs among vertebrate species from cardiac evolution point of view [49]. First appearance of a chambered heart could be observed in the jawless fishes (agnathans) [50] followed by development of a conus arteriosus in cartilaginous fish, with its presence also in teleost fish [51]. Then comes the first full atrial septation in lungfish [52] and evolution continues with the transition to the terrestrial life-style in amphibians, where the metamorphosis plays the main role in cardiovascular evo-devo [53]. In Sauropsids, which cover the reptilian and avian lineages [54], there is a great diversity in cardiac structures such as numbers of chambers and levels of ventricular septation [55] from spongy hearts in geckos or agamids, e.g. Leopard gecko (*Eublepharis macularius*) or Central bearded dragon (*Pogona vitticeps*), without ventricular septation [56]. These species, with similar cardiovascular system [56,57], however, represent different life-histories [58,59] and their positions in squamates phylogenetic tree differ with the closeness of Central bearded dragon to monitor lizards in comparison to basal leopard gecko [60]. Another peculiar feature in squamate cardiovascular system lies in presence of almost septated ventricle in pythons [61] and monitor lizards [62], which could be the plesiomorphic state between snakes and varanids [63,64]. The final milestone is the full ventricular septum in archosaurs – crocodylians, dinosaurs, and birds [65] as well as in mammalian lineages [66] as a result of convergent evolution [67]. This crown lineage, termed as Archosauria [68], is characterized by a fully septated ventricle in Crocodylia and Aves [69], because birds are the sister group to crocodylians [70]. In dinosaurs, which are generally viewed as part of archosaurs [71], the fossil record of the heart is not known because soft tissues and organs do not fossilize easily [72]. Nevertheless, it is premised, that the cardiovascular system could be similar to the avians and crocodylians [73] and all lineages are probably originally endothermic [74]. It should be noticed here, that the synapsid (mammalian) heart is also bearing the reptilian features such as presence of the sinus venosus in, e.g., Monotremata [75] which are an important part of the synapsid lineage [76]. Moreover, sinus venosus is also presented in placental hearts as *sinum venarum* [77] in the right atrium, even in humans [78]. However, there are also differences among sauropsid (reptiles and birds) and synapsid (mammals)

lineages in terms of cardiac evolution, especially in both aortic arches present in reptiles, in the right aortic arch presents in birds, and in the left aortic arch presents in mammals [79] or in the presence of a fully developed cardiac conduction system convergently evolved in birds and mammals [80].

The most conspicuous anatomical variation in the hearts is in the number of PVs. The human heart has four PVs, however, mouse [81] and chick have only one PV entering the LA with a solitary orifice. The development of the pulmonary venous connections is similar in the chick, the mouse, and the man [82]. When we compare the atria of different species, we can find a different level of trabeculation. Zebrafish has a more complex structure of the PM compared to mouse or human. There is a difference in development of PM between mouse and human, as there is evidence that during mouse development, the PM develop in both atria simultaneously, but this is not the case in human, where the RA acquires PM prior to the LA [7]. The shape of the heart varies with the body size as well as the location of the heart in the body. It is also connected to the heart rate. Generally speaking, the faster frequencies are found in species with smaller size and, similar to human, in young animals the heart rate is higher comparing to the adults. The other noticeable difference is a different ratio between atrium and ventricle. The size of the atrium, its function, and frequency can show a certain relationship. For example, a fin whale has heart rate around 9 beats per minute so there is a need for bigger atria because of their function as a blood reservoir during ventricle systole, and therefore, for bigger heart. In comparison, heart rate of a hummingbird can be up to 1200 beats per minute so there is not so high blood volume coming into the atria during ventricular contraction and the atria can thus be relatively smaller.

The development of cardiac atria

It is important to understand how the atrial chambers and their parts develop during embryogenesis. The data are quite limited, but we already have some insights into the process. The definitive atrial chambers and their parts do not all form from the same embryonic tissues. First, the embryo is formed into a disc with the primitive streak. This is found at Carnegie stage (CS) 7, which corresponds to approximately 16 days of human development. Then, during gastrulation, there are cells migrating from the sides of the streak to so-called heart-forming regions, which are located on both sides of the midline of the disk [81]. It is already known that there are two waves of migrations of these cells. The first lineage forms the primary cardiac crescent, which does not contribute cells for the entire heart tube. Thanks to advanced molecular techniques, it has been found that there is also a secondary heart lineage. These two lineages give rise to different structures. The precursor cells for the atrial chambers come from both lineages, same as the origin of the right ventricle, but the majority of cells comes from the second lineage. Left ventricular precursor cells are provided from the primary cardiac crescent and the outflow tract is derived exclusively from the second lineage [81]. The formation of the atrial chambers is one of the many steps during heart transformation into a four-chambered organ and they form up to CS11 (around 22 days) [83]. After migration of the precursor cells, the heart tube represents the first step in heart formation. The tube elongates by addition of the second heart field cells; as a result, it bends to the right side, loosing its initial symmetry. This phase is called cardiac *looping*. The development of the atrial chambers, as well as ventricular ones, is known as *ballooning*. It is an expansion of the pouches from the primary heart tube, underlined by myocyte proliferation. At the inlet of the tube, the incorporation of the draining channels forms the primordium for formation of both definitive atrial chambers. The myocardium that forms the walls of the pouches conducts the cardiac impulse more rapidly compared to the primary myocardium that forms the wall of the heart tube [81]. The venous components come from different embryonic tissues [3]. The systemic veins become a part of the heart as the primordium of a common atrium, with its right and left halves determined by the persisting connection to the embryonic body through the dorsal mesocardium. The right and left atrial pouches differentiate from the common atrium to the sides of the developing arterial pole [81]. The development of the PV is delayed compared to the formation of the systemic venous tributaries. Venous components start to form around 4 weeks of human development. In human embryonic development around 4 weeks of gestation (CS12), the lungs are not yet developed, so pulmonary venous structures are not present. Some researchers state that the first sign of PV is seen in CS13 (approximately 28 days) [83] and during the beginning of the 5th week of gestation as an invagination of the posterior wall of the LA into the dorsal mesocardium [84], but this still remains controversial. In the dorsal mesocardium, the PV canalizes

from a mid-pharyngeal strand at around 6 weeks of development in the human and opens into the atrium between the ridges marking the site of the dorsal mesocardial connection [85]. The pulmonary venous channel can be distinguished at approximately CS12 (4th week of gestation) [81] and from the evidence we have from studies performed on mouse, it becomes evident that the PV is formed from different tissue than the tributaries of the systemic venous sinus [86]. The data show that the origin of PV is from the mediastinal myocardium, which is the same as for the atrial septum [3]. The evidence of connections between the LA and PVs is at Carnegie stage 14 (5th week of gestation) [7]. The beginning of atrial septation corresponds the emergence of the primary atrial septum (*septum primum*), which happens during CS14 to CS16 (5th to 6th weeks) [83,87].

Molecular markers of atrial development

Two proteins help us to distinguish between the primary myocardium and chamber myocardium. The first one is connexin40, which is a major gap-junction protein in the atrial myocardium [88] and the other one is natriuretic precursor peptide also known as atrial natriuretic peptide (ANP). Both can be found in the chamber (secondary) myocardium, but none in the primary one. When we look closely at the different parts of the heart, these proteins help us to clarify their origin. The atrial pouches, as well as the apical parts of the developing ventricles, are positive for connexin40 and ANP. These findings show that those structures are derived from the secondary myocardium. The atrioventricular canal and the walls of the systemic venous components are both negative for both markers, so their origin is from the primary (tube) myocardium. Parts localized in the dorsal mesocardium stain positively for connexin40 and negatively for ANP. Such part of the myocardium is called the *mediastinal myocardium*, which is distinct from both the primary and secondary one. Such combination is found in the PV and its myocardium, which is connexin40 positive but ANP negative, therefore, it is a fast-conducting myocardium and not the slowly-conducting primary myocardium [81]. Another useful marker is *pitx2*. This marker stains positively the sites that express the gene determining morphological leftness [81]. Thus, only the future LAA stains positive. The primary atrial septum stains positively only for connexin40 and divides the common atrium into two parts. It also stains positively for *pitx2* which shows that it originates from the left side [81].

The atrial function and clinical pathophysiology

Although the function of the ventricles was extensively studied and is the major subject of clinical echocardiographic evaluation, the atria received less attention.

The atria serve 3 main hemodynamic functions during cardiac cycle [89]:

1. **Blood reservoir** during ventricular systole.
2. **Conduit** between caval/pulmonary veins and ventricles in early diastole.
3. **Contractile chamber** in late diastole.

The early phase of LA reservoir function is assisted by descent of mitral/tricuspid valve anulus in systole which causes suction of blood to the respective atrium [90]. The atrial reservoir function is also influenced by atrial compliance [91].

The cardiac diastole is divided into 3 phases:

1. phase of rapid ventricular filling corresponding to atrial conduit function.
2. diastasis with equilibration of pressures between atria and ventricles.
3. phase of late diastolic filling provided by the atrial contraction.

Atrial contraction results in the so-called atrial kick (AK), which adds the volume to ventricles in late ventricular diastole that contributes up to 20-30 % of total volume in total cardiac output (CO) [92]. The loss of AK can be caused by atrioventricular dissociation and is called atrioventricular uncoupling [93]. The typical scenario of a lack of AK and, therefore, changes in hemodynamics, is seen in patients with AF. The atrial wall is moving quickly with the high frequency during AF and the atria are thus not able to pump blood effectively to the ventricles [94].

A different situation occurs in junctional ectopic tachycardia, where the atria are activated retrogradely through the AV node and contract during ventricular contraction when are the atrioventricular valves closed. This results in retrograde AK to the caval and pulmonary veins – so-called “cannon waves” in central venous pressure monitoring [95]. Another type of atrioventricular uncoupling is seen in a first-grade atrioventricular block. Atria contract too early in diastole, interfering with the rapid filling phase. The long period of equilibrated pressures between atria and ventricles, corresponding to

the long PR interval on the ECG results in late diastolic regurgitation of the atrioventricular valves [93]. Loss of AK is generally well tolerated in an otherwise well-functioning heart. However, in patients with already impaired ventricular function, or in patients with a less compliant ventricle (due to hypertension, aging, or fibrosis) that is much more dependent on the atrial contribution, it could lead to a decreased CO. This can be seen in patients with AF, AV block, univentricular circulation or after surgical correction of complex congenital heart diseases. This is the reason why a restoration of atrial rhythm by cardioversion, or atrial pacing in a case of dissociation between the contraction of atrium and ventricle can improve atrioventricular synchrony and increase CO [96].

The heart also serves as an endocrine organ as the LA contains sensors which asses the volume of blood and release the ANP in response to fluid overload [97]. The atria, particularly in the compliant appendages, are also densely innervated by autonomic nerves that participate in volume sensing. Francis A. Bainbridge discovered during his experiment on dogs in 1915 a reflex increasing the heart rate as a consequence of increased volume of blood which is detected by baroceptors located in both atria. However, the most important component of this reflex is the right-sided baroreceptors [98].

In clinical practice, the function of the atria can be assessed by echocardiography or by catheterization; for research purposes, atrial function can be more precisely assessed by simultaneous pressure-volume (PV) analysis (Fig. 4). The maximal volume of the atrium indexed to body size (left atrial volume index, LAVI), that is calculated from 2D echocardiography, is considered as basic but non-specific marker of the atrial function and its hemodynamic loading. The more specific indicators are derived from spectral pulsed Doppler imaging of ventricular filling – a late active filling phase representing atrial contraction (A-wave), the peak velocity of the A-wave and its velocity time, the atrial fraction, and the atrial ejection force. (Fig. 4A) The peak A-wave velocity is influenced by heart rate, loading conditions and normal aging [90]. 2D speckle-tracking imaging has been recently used as one of the methods to assess deformation of the atria. The software calculates the longitudinal strain and strain rate for each segment of the atrium, which provides us with data about physiological features regarding atrial functions (Fig. 4B) [99]. Some of the conditions i.e. pulmonary hypertension can be associated with impaired reservoir and conduit function but enhanced active contractile function [100].

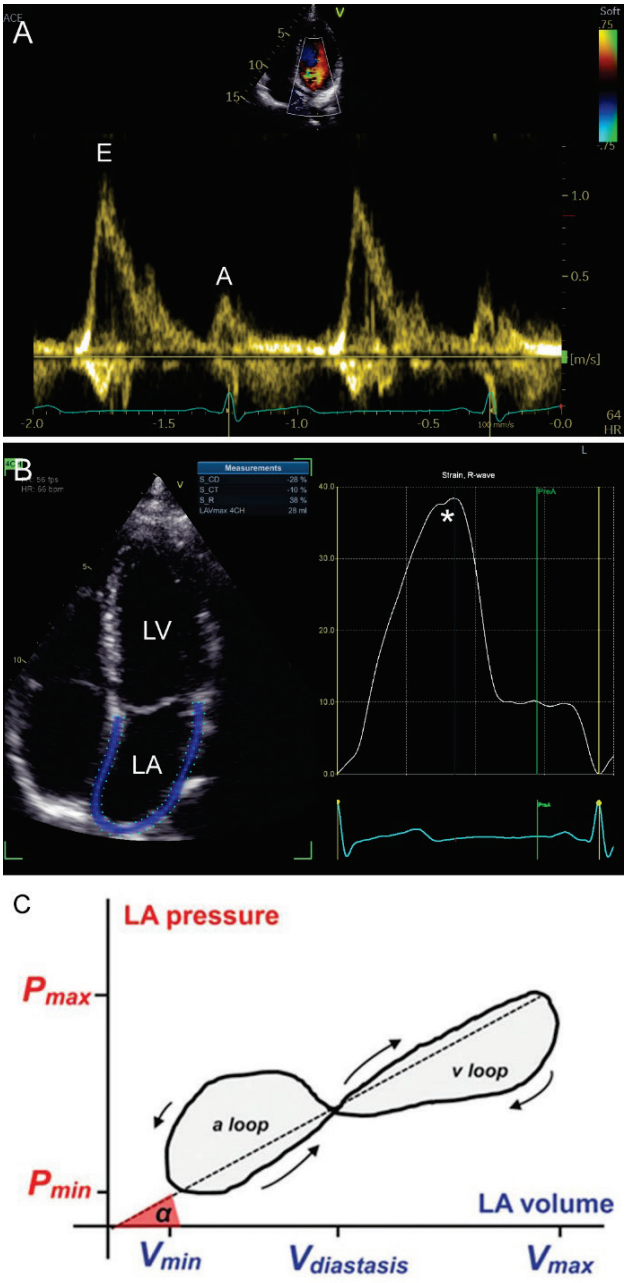

Fig. 4. The echocardiogram showing (**A**) transmitral Doppler flow representing filling of the left ventricle, (**B**) 2D speckle-tracking imaging assessing the LA where peak of the curve (*) shows the LA reservoir function, (**C**) PV loop of the LA (from Melenovsky *et al.* [109]; LV = left ventricle, LA = left atrium, E = the passive filling of the ventricle during diastole, A = the late active filling phase representing atrial contraction, P = pressure, V = volume, a loop = atrium loop, v loop = ventricle loop, *α* = LA stiffness is represented by slope of dashed line that connects maximal and minimal pressure-volume points.

PV loop (Fig. 4C) is a graphic, which gives information about changes between atrial pressure and volume during the cardiac cycle. The atrial PV loop is different from the ventricular loop. The ventricular loop contains information on different phases of the cardiac cycle such as ventricular

filling, isovolumic contraction, ejection and isovolumetric relaxation, the phases which take places during diastole and systole [101]. The atrial PV loop represents the reservoir, conduit and stroke volume that correspond to almost every purpose of the atrium [102].

The RA is an important structure for cardiologists. In addition to containing the cardiac pacemaker and its importance during surgeries, it is also the implantation site of atrial leads during placement of cardiac pacemaker. The coronary sinus in the RA allows to transvenously reach lateral wall of the left ventricle to place there a lead for chamber resynchronization pacing (cardiac resynchronization therapy) in patients with damaged ventricular conduction. In patients with right ventricular overload or right heart failure, the right atrium dilates, develops hypertrophy, and even more contributes to work of the right heart; the loss of right atrial mechanical function due AF has then particularly detrimental effects. In a diseased heart, RA is also the place of atrial flutter – a common macro-reentrant tachycardia that goes through cavotricuspid isthmus; the application of radiofrequency (RF) energy (RF ablation) of this isthmus eliminates atrial flutter. The right atrium can also be a location for thrombi formation, which could lead to pulmonary embolism and in the settings of PFO to paradoxical embolism into the systemic circulation (e.g. may lead to stroke).

The LA is frequent site for development of arrhythmias, most often AF. Long-term exposure of the atrium to increased hemodynamic stress leads to changes in atrial cardiomyocytes and extracellular matrix, inflammation, tissue fibrosis and increased electrical heterogeneity, thus favoring the persistence of micro-reentrant circuits of AF [103-105]. While foci of ectopic activity in PVs are necessary for initiation of AF (as described above), structural remodeling of atrial tissue is necessary for AF persistence [34]. Localized application of RF ablation to the atrial tissue leads to interruption of conductive properties of the atrial myocardium without loss of structural integrity. With this approach, applied percutaneously *via* a transvenous catheter, it is possible to electrically isolate PVs from atria and prevent AF initiation [32]. Simultaneously it is also possible to create linear lesions in the LA that prevent persistence of AF. Such ablation therapy represented a breakthrough in treatment of AF and very often lead to complete elimination of the arrhythmia. Besides RF energy or cryoablation, the application of pulsed field energy now appears to be an even more effective approach how to create non-conducting lesions in the atria [106]. Given the fact that AF is the most common of arrhythmias and is associated with considerable morbidity and mortality due to risk of stroke or heart failure [107], it is evident that effective treatment of AF by catheter-delivered therapies attracted enormous interest in the medical community.

The LA has also important role during development of heart failure, particularly in patients with impaired diastolic function [108,109] and in patients with heart failure with preserved ejection fraction of the left ventricle (HFpEF) [110]. The LA can increase its work and help to maintain normal filling of the less compliant left ventricle. Over time, this atrial adaptation may be lost due to ensuing atrial myopathy, leading to worsened diastolic function of the left ventricle. Loss of mechanical function of the LA, even in patients with preserved sinus rhythm, may be the final step that converts asymptomatic left ventricular hypertrophy into symptomatic left heart failure, and this is particularly pronounced in patients with HFpEF [110,111].

Besides the role in contraction, the LA serves as volume buffer that facilitates oscillatory filling of the ventricle and prevents pressure and flow oscillations to propagate backwards into the pulmonary circulation. Loss of atrial compliance, due to shrinkage or increased wall stiffness (stiff left atrial syndrome), leads to remodeling of the small pulmonary vessels with development of precapillary pulmonary hypertension [112].

Summary

To sum up, the atria are a frequent site of ablation or catheterization procedures, however they have not received comparable amount of attention comparing to the ventricles. Since RA contains the SA and the AV node, it is very important for clinicians to know the morphology of the atria. The LA and RA have the same main parts such as the vestibule, the venosus part and the appendage, but differ morphologically. One of the structures which we focused on are PM located in the LAA and the RAA, which may be homologous to the trabeculae in the ventricles. The atrial function is also not negligible, as it can play a significant role in CO in the heart with impaired function.

Conflict of Interest

There is no conflict of interest.

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