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Pathophysiology of atrial fibrillation. Systemic review

Patofizjologia migotania przedsionków. Przegląd systemowy

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Abstract

Atrial fibrillation (AF) is an arrhythmia in which chaotic electrical signals are generated in the atria. AF can be classified as first episode AF, paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF. Hence, AF is one of the biggest problems of contemporary health care (due to severe complications like thromboembolic disease and huge expenses associated with the treatment).

The pathophysiology of the AF includes a triggered activity in the myocardium and also left atrial enlargement (LAE), and remodelling of the atria that may result in an interatrial block (IAB). IAB is prolonged conduction between the atria and is diagnosed in electrocardiography (ECG) when P-wave duration ≥ 110 ms. Other ECG changes coexisting with IAB, LAE and also remodelling of the atria are attributed to P-wave dispersion ≥ 40 ms, and a P-wave terminal force in V1 ≤ –0.04 mm/s.

Remodelling of the atria leads to structural, cellular and hormonal changes. At the cellular scale — mitochondrial size and count are enlarged. A neurohormonal imbalance is also related to arrhythmia. An increased level of atrial natriuretic peptide, B-type natriuretic peptide, angiotensin II, transforming growth factor-β_1 are observed in the case of cellular and ion channels changes.

Atrial fibrillation is a significant problem posed to modern health care. In light of these remarks, an effective way of AF prevention needs to be found. In any case, further research in this field is needed.

Key words: atrial fibrillation, interatrial block, electrocardiography

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Introduction

Atrial fibrillation (AF) is an abnormal and irregular heart rhythm in which electrical signals are generated chaotically throughout the atria. AF can be classified as first episode AF, paroxysmal AF (that terminates < 7 days), persistent AF (AF sustained > 7 days and early persistent AF — lasting less than 3 months), long-standing persistent AF (> 12 months in duration), permanent AF (accepted by the patient and physician) [1]. One of the most frequently identified predictors of AF is a visibly prolonged time for the signal to appear. It is called the interatrial block (IAB).

Due to the fact that AF is the most common type of heart arrhythmia, it is one of the biggest problems of the present health care system. AF is reported to cost the United States alone approximately $6 billion each year. Reports indicate that people who suffer from AF spend an additional $8,705 more per year than people without AF [2, 3]. It is estimated, that by 2050 AF will have affected 6–12 million people in the USA and 17.9 million people in

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Europe by 2060 [4]. Currently, AF affects circa 2.9% of the world's adult population. Among people within the range of 60–69 years old — AF occurs in 4.2% of the population. AF affects also 9.7% of the population from the age group of 70–79, whereas if focusing on people from within the group of 80–89 years old, AF is noted to affect 13,4% of them [5]. Hence, LAE and remodelling may result in AF. In electrocardiography (ECG) it can be demonstrated as an interatrial block (IAB).

Interatrial block — definition and consequences

The interatrial block is prolonged conduction between the atria. It is diagnosed in ECG when P-wave duration ≥ 110 ms IAB is caused by the enlargement of the atria and atrial remodelling. Impulse delay or blockage is often in the Bachmann bundle (BB) [6]. The first research in this field was done by Bachmann et al. in 1916 — interatrial conduction delay was pointed out and its importance as leading to atrial fibrillation was mentioned [7]. IAB is an important sign because it has serious implications. First of all, IAB is associated with AF, but the role of the interatrial block as a predictor of other arrhythmias has not been evaluated [8]. Secondly, remodelling of the left atrium could lead to cerebral stroke, even if AF is not manifested [9]. That is why, in 2005, Lorbar et al. showed an 80% prevalence of IAB in patients with embolic stroke [10].

Drawing an analogy to other conduction delays, IAB may be graded as first, second and third degrees. IAB can also be divided into partial and advanced type of block [11] The normal transit time for electrical impulses generated in the sinus node has to be conducted throughout the atria in less than 110 ms. The first degree IAB (or partial IAB) is a conduction delay across the Bachmann's bundle with P-wave duration > 110 ms. The impulse goes with a delay through the normal conduction pathway. IAB with notched P-wave in leads I, II, III and aVF is considered to represent partial or first degree. In ECG P-wave morphology in lead V1 in partial IAB often comes with a negative mode (or a biphasic mode), however, left atrial enlargement cannot be diagnosed. The second degree of IAB is diagnosed when the first component of the P-wave maintains its spatial orientation while the final component of IAB shows noticeable modifications in its morphology and duration (this state is also seen with atrial aberrancy), but conditions of the third degree of IAB are not met. The third degree of IAB is a complete block in the normal interatrial conduction pathway. The impulse goes through an alternate pathway with caudocranial activation of the left atrium. ECG biphasic (±) (±) P-wave in the inferior leads is therefore produced. A negative P-loop is more evident than in partial IAB, what is often intensified by coexistent left atrial enlargement. That is why the terminal negative loop of P-wave in lead V1 is wider as compared with a partial IAB. Due to the underlying fibrosis, the positive mode of P-waves in leads II, III and aVF may sometimes not be well seen [11–13].

Remodelling of the atria

Remodelling can be divided into three separate types: electrical, structural, and autonomic. Structural remodelling is the cause of electrical dissociation between local conductive heterogeneity and muscle fibre bundles. This state results in the re-entry of waves and arrhythmias. Due to the fact, that structural remodelling is usually irreversible, it is important to start treatment very early [14]. Various aetiologies of remodelling should be considered to understand this process (changes in intracellular structure in cardiac muscle, left atrium enlargement as a cause of fibrosis, *etc.*) because changes in the cardiac tissue structure depend on the mechanism of atrial remodelling. In the case of atrial fibrillation myocyte, myolysis is additionally observed [15]. In the case of left atrial enlargement associated with heart failure — fibrosis and myocyte cellular hypertrophy are observed [16]. Fibrosis of the atrium plays a great role in the pathogenesis of AF. Daccarett et al. [17] confirm this point of view in research performed with magnetic resonance imaging (MRI). They declare, that the extent of fibrosis is an independent risk factor of cerebral stroke.

Cellular changes in atria remodelling

At the cellular scale — mitochondrial size and count are enlarged. These changes appear after about one week of continued atrial fibrillation [18]. What is more, in the case of healthy myocytes, visible domination of myosin heavy chain (α isoform) can be observed, while in the cases of heart failure the amount of myosin heavy chain β isoform increase. This is the reason for a decrease of left atrial systole connected with higher left atrium (LA) volume. These factors are directly responsible for LA remodelling. After this stage is completed, degenerative changes in myocyte cells can be found *e.g.* cellular oedema, the nucleus pyknosis and in consequence — lower count of myocyte cells [19]. Furthermore, to create a re-entry wave — a refractory period should be shortened, conduction should be delayed and the conduction itself should be elongated. A great role in these changes plays ion-channel remodelling [20]. The atrial refractory period depends on the duration of electric potential because sodium (Na^+) channels are inactivated in the depolarization phase and need repolarization to –60 mV. The duration of electric potential is determined by a balance between inward current (especially of Ca^{2+}) and outward flow of K^+. The electric remodelling of ion channels can lead to shortening of both the resting potential in a cardiomyocyte and the refractory period. Rapid left atrial activation (during AF), reduces the inward current

Ca^{2+} of type L, and escalates the outward flow of K^{+}. If the new impulse strikes into the unidirectional block, re-entry wave can be developed, which also leads to atrial fibrillation [21]. These changes are the main symptoms leading to AF propagation [22, 23].

Left atrial enlargement — mechanisms and implications

Zacà et. al. confirms that the increased size of the LA predicts atrial fibrillation. What is more, LA progressive enlargement is examined as a predictor of arrhythmic recurrences [23]. On the other hand atrial enlargement can be a result of atrial fibrillation [24]. In ECG left atrial enlargement is diagnosed by P-wave duration > 120 ms long, or alternatively, the time between its two peaks ≥ 40 ms and by positive-negative (or negative) P-wave in V1 [25]. An increased anterior-posterior (AP) diameter of left atrium signed in M-mode echocardiography is related to increase AF incidence by 40% [26] An AP diameter over 5 cm, when sinus rhythm is maintained, characterizes a 4-fold increase risk of AF [27]. Additionally, LA volume is a clear indicator of AF in patients with cardiomyopathy, and the same set of parameters apply to elderly patients [28]. Unfortunately, the relationship between planimetric diameters and the volume of LA is not linear [29]. The volume of AF is found to be a better tracer of atrial fibrillation determined by left atrium volume index (LAVI) — LA volume measured by biplane area length method and indexed to body surface area (BSA) [30]. Left atrial enlargement contributes to the growth and preservation of arrhythmia, which is called electrophysiological remodelling. On the other hand, arrhythmia leads to structural changes in the cardiac muscle [31]. That is why maintained sinus rhythm is responsible for a decrease of left atrial diameter and contractility enhancement [32]. Xiong et al. suggest there are no differences of LA diameters before cardioversion and directly after the procedure [33]. Nevertheless, measurements performed one month after the appearance of sinus rhythm showed a decrease of AP diameter of LA. What is more, the reduction of an LA size is related to Interventricular septal motion [34]. Tops et al. [34] proved that electrical cardioversion or cardiac ablation leads to a decrease of an LA size, however, the recurrence of AF undermines these changes. Another research demonstrates LA volume decrease after effective cardiac ablation from 59 to 50 mL in cases of patients, who maintain sinus rhythm for 3 months. In the case of patients who are after the ineffectual procedure, the recorded LA volume increases from 63 mL to 68 mL. Restored sinus rhythm results with a reduction of left atrial AP diameter from 4.5 ± 0.3 cm to 4.2 ± 0.2 cm ($p < 0.001$), and a reduction of the LA area from 29.4 ± 5.1 cm^2 immediately after electrical cardioversion to 26,7 ± 4,6 cm^2 after 6-month follow-up [35]. Similar results are presented by Reant et al. [35] who proved that in the case of patients with persistent AF, after the restitution of sinus rhythm in 11-month follow-up occurred decrease LA area from 28,7 ± 2,8 cm^2 to 21,7 ± 2,1 cm^2 (24% reduction). Unfortunately, patients with an AF recurrence during the 11-month follow-up achieved a 7% reduction in the LA area. What is more, in a situation of a recurrent, paroxysmal AF after effective cardiac ablation a 19% reduction of the LA area is possible (from 23.5 ± 4.8 cm^2 to 19.0 ± 3.8 cm^2), while, in cases, after electrical substrate elimination is not total — the reduction of the LA area is successful in the case of only 5% of the total number of patients. These findings prove that even short duration of AF stimulates LA remodelling. On the other hand, maintenance of sinus rhythm is helpful in averting pathological remodelling, even if AF is recurrent. Furthermore, there is a relationship between electrical and structural remodelling [36]. Surgical procedures (*e.g.* Maze procedure) also conduce to a decrease of LA area and the associated advantageous biochemical changes [37].

Neurohormonal imbalance in the interatrial block

Neurohormonal changes play a significant role in atrial remodelling. An increased level of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), angiotensin II, transforming growth factor-β_1 (TGF-β_1) are all related to both cellular and ion channels changes [38]. In the case of patients with AF, the level of C-reactive protein (CRP) is elevated, as well as tumour necrosis factor, interleukins and cytokines. The significance of inflammation in the pathogenesis of cardiac muscle remodelling is verified by relations between LA volume and the level of CRP in peripheral blood [39]. Due to the fact, that there is a relationship between elevated CRP and metalloproteinases activation (by oxygen free radicals), inflammation is found to influence LA fibrosis. That leads to a left atrium enlargement and a deterioration of the LA mechanic function. Moreover, CRP stimulates the expression of the receptors of end glycation products, which, in turn, leads to hardening of arterial walls and the cardiac wall. That is the reason for left atrial distention to appear in the case of patients who suffer from diabetes mellitus [39].

Electrocardiographic changes

ECG is a crucial diagnostic instrument in cases of atrial fibrillation, interatrial block and enlargement of the atria. P-wave terminal force shows early delay in left atrial conduction (it is a product of the amplitude and the duration of the terminal phase of P-wave in lead V1). It has been observed when left atrium is dilated [32]. The P-wave initial portion in the same lead is significantly greater

in patients with left atrial overload. These patients are more likely to develop AF in the future. P-wave duration ≥ 125 ms, P-wave dispersion ≥ 40 ms, and a P-wave terminal force in V1 ≤ –0.04 mm/s are good clinical risk factors of the atrial fibrillation recurrence, post pulmonary vein isolation (PVI) in the case of patients with paroxysmal atrial fibrillation [40]. De Bacquer et al. [15] checked baseline P-wave items in patients aged 55 to 74 years and apparently healthy at baseline. 40 of them developed AF within the 10-year period and they were compared retrospectively with those of 120 matched controls. Broad maximum P-waves (> 120 ms) at baseline were observed in 70% of the patients with AF and it referred to 41% of controls (p = 0.002). P-wave duration proved to be a significant risk marker (independent of other risk factors like blood pressure, body mass index etc.). Ishida et al. [16] checked the incidence of AF in patients with marked LA overload (diagnosed by P-wave inversion in lead V1) which was 15-fold higher than that in control patients (19% of patients with LAO developed AF versus 81 % who did not. In the control group under discussion — AF was developed by 1.3% of patients). On the other hand, no significant difference was seen between the AF and non-AF groups with regard to the area, duration, and amplitude of the P-wave terminal portion in lead V1. Alternatively, these ECG changes were significantly greater in the AF group than in the non-AF group. In view of this, the area of the P-wave initial portion was independently associated with the development of AF (hazard ratio 4.02, 95% confidence interval 1.25–17.8; p = 0.018) [16].

Conclusions

Atrial fibrillation is a significant problem posed to modern health care. Huge expenses incurred by AF occurrences together with thromboembolic implications of AF create a pressing need for finding a way to prevent the condition. Well-known risk factors *e.g.* LAE, age, previous history of AF do not reduce the range of problems related to the prevention of AF. The pathophysiology of the AF includes LAE, remodelling of the atria (that may result in interatrial block) and also triggers activity in cardiac muscle. P-wave duration ≥ 125 ms, P-wave dispersion ≥ 40 ms and a P-wave terminal force in V1 ≤ –0.04 mm/s appear to be good clinical factors indicating interatrial conduction delay and left atrial enlargement. In any case, further research in this field is needed.

Conflict of interest

The authors declare no conflict of interest.

Streszczenie

Migotanie przedsionków (AF) jest arytmią, która charakteryzuje się chaotycznymi impulsami elektrycznymi generowanymi w przedsionkach serca. Można wyróżnić pierwszy epizod AF, napadowe AF, przetrwałe AF, przetrwałe długotrwające AF, utrwalone AF. Obecnie jest to jeden z największych problemów ochrony zdrowia (np. ze względu na ciężkie powikłania zakrzepowo-zatorowe i ogromne nakłady finansowe związane z ich leczeniem).

Mechanizm powstania AF polega na wyzwalaniu aktywności miokardium na podłożu powiększenia i przebudowy przedsionków. Mogą one skutkować blokiem przewodzenia (IAB) lub wydłużonym czasem przewodzenia między przedsionkami (LAE). Diagnostyka LAE jest możliwa na podstawie elektrokardiogramu (EKG), gdy czas trwania załamka P przekracza 110 ms. Inne zmiany w EKG współwystępujące z blokiem śródprzedsionkowym, powiększeniem lewego przedsionka, a także związane z remodelingiem przedsionków są wyrażone poprzez dyspersję P ≥ 40 ms i iloczyn amplitudy i czasu trwania fazy ujemnej P w odprowadzeniu V1 ≤ –0,04 mm/s.

Remodeling przedsionków prowadzi do strukturalnych, komórkowych i hormonalnych zmian. W skali komórkowej zwiększają się liczba i rozmiar mitochondriów. Zaburzenie równowagi neurohormonalnej również jest związane z arytmią. Podwyższone stężenia przedsionkowego peptydu natriuretycznego, peptydu natriuretycznego typu B, angiotensyny II, transformującego czynnika wzrostu β_1 towarzyszą zmianom komórkowym i modyfikacjom kanałów jonowych.

Migotanie przedsionków to bardzo ważny problem, będący wyzwaniem współczesnej ochrony zdrowia. W związku z tym należy poszukiwać metod efektywnej prewencji tej arytmii.

Słowa kluczowe: migotanie przedsionków, blok śródprzedsionkowy, elektrokardiografia

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References

1. Allessie MA, de Groot NMS, Houben RPM, et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. Circ Arrhythm Electrophysiol. 2010; 3(6): 606–615, doi: 10.1161/CIRCEP.109.910125, indexed in Pubmed: 20719881.
2. January CT, Wann L, Alpert J, et al. 2014 AHA/ACC/HRS Guideline for the maanagement of patients with atrial fibrillation. Circulation. 2014; 130(23), doi: 10.1161/cir.0000000000000041.
3. Mozaffarian D, Benjamin E, Go A, et al. Heart dsease and stroke statistics — 2015 update. Circulation. 2015; 131(4), doi: 10.1161/cir.0000000000000152.
4. Lloyd-Jones D, Adams R, Carnethon M, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics — 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009; 119(3): 480–486, doi: 10.1161/CIRCULATIONAHA.108.191259, indexed in Pubmed: 19171871.
5. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. J Intern Med. 2013; 274(5): 461–468, doi: 10.1111/joim.12114, indexed in Pubmed: 23879838.
6. Chhabra L, Devadoss R, Chaubey VK, et al. Interatrial block in the modern era. Curr Cardiol Rev. 2014; 10(3): 181–189, doi: 10.2174/1573403x10666140514101748, indexed in Pubmed: 24827803.
7. Bachmann G. The Inter-auricular time interval. Am J Physiol. 1916; 41(3): 309–320, doi: 10.1152/ajplegacy.1916.41.3.309.
8. Baranchuk A, Enriquez A, Antiperovitch P. Advanced interatrial block as a key marker for atrial fibrillation recurrence: Bayés' syndrome. J Geriatr Cardiol. 2017; 14(3): 169–173, doi: 10.11909/j.issn.1671-5411.2017.03.005, indexed in Pubmed: 28592959.
9. Hashimoto N, Watanabe T, Tamura H, et al. Left atrial remodeling index is a feasible predictor of poor prognosis in patients with acute ischemic stroke. Heart Vessels. 2019; 34(12): 1936–1943, doi: 10.1007/s00380-019-01445-7, indexed in Pubmed: 31168655.
10. Lorbar M, Levrault R, Phadke JG, et al. Interatrial block as a predictor of embolic stroke. Am J Cardiol. 2005; 95(5): 667–668, doi: 10.1016/j.amjcard.2004.10.059, indexed in Pubmed: 15721117.
11. Kitkungvan D, Spodick DH. Interatrial block: is it time for more attention? J Electrocardiol. 2009; 42(6): 687–692, doi: 10.1016/j.jelectrocard.2009.07.016, indexed in Pubmed: 19698951.
12. Ariyarajah V, Asad N, Tandar A, et al. Interatrial block: pandemic prevalence, significance, and diagnosis. Chest. 2005; 128(2): 970–975, doi: 10.1378/chest.128.2.970, indexed in Pubmed: 16100193.
13. Bayés de Luna A, Platonov P, Cosio FG, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. J Electrocardiol. 2012; 45(5): 445–451, doi: 10.1016/j.jelectrocard.2012.06.029, indexed in Pubmed: 22920783.
14. Shinagawa K, Shi YF, Tardif JC, et al. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. Circulation. 2002; 105(22): 2672–2678, doi: 10.1161/01.cir.0000016826.62813.f5, indexed in Pubmed: 12045175.
15. De Bacquer D, Willekens J, De Backer G. Long-term prognostic value of P-wave characteristics for the development of atrial fibrillation in subjects aged 55 to 74 years at baseline. Am J Cardiol. 2007; 100(5): 850–854, doi: 10.1016/j.amjcard.2007.04.017, indexed in Pubmed: 17719332.
16. Ishida K, Hayashi H, Miyamoto A, et al. P wave and the development of atrial fibrillation. Heart Rhythm. 2010; 7(3): 289–294, doi: 10.1016/j.hrthm.2009.11.012, indexed in Pubmed: 20133209.
17. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol. 2011; 57(7): 831–838, doi: 10.1016/j.jacc.2010.09.049, indexed in Pubmed: 21310320.
18. Zapolski T, Kamińska A, Wysokiński A. Atrial fibrillation and left atrium remodelling — pathophysiology and prognostic implications. Post Nauk Med. 2015; 27(8B).
19. Sanfilippo AJ, Abascal VM, Sheehan M, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation. 1990; 82(3): 792–797, doi: 10.1161/01.cir.82.3.792, indexed in Pubmed: 2144217.
20. Nattel S, Maguy A, Le Bouter S, et al. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev. 2007; 87(2): 425–456, doi: 10.1152/physrev.00014.2006, indexed in Pubmed: 17429037.
21. Yue L, Feng J, Gaspo R, et al. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res. 1997; 81(4): 512–525, doi: 10.1161/01.res.81.4.512, indexed in Pubmed: 9314832.
22. Cha TJ, Ehrlich JR, Chartier D, et al. Kir3-based inward rectifier potassium current: potential role in atrial tachycardia remodeling effects on atrial repolarization and arrhythmias. Circulation. 2006; 113(14): 1730–1737, doi: 10.1161/CIRCULATIONAHA.105.561738, indexed in Pubmed: 16585394.
23. Zacà V, Galderisi M, Mondillo S, et al. Left atrial enlargement as a predictor of recurrences in lone paroxysmal atrial fibrillation. Can J Cardiol. 2007; 23(11): 869–872, doi: 10.1016/s0828-282x(07)70841-3.
24. Kozłowski D. Method in the Chaos — a step-by-step approach to ECG Interpretation. Eur J Transl Clin Med. 2018; 1(1): 74–87, doi: 10.31373/ejtcm/92255.
25. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. J Intern Med. 2013; 274(5): 461–468, doi: 10.1111/joim.12114, indexed in Pubmed: 23879838.
26. Davies MJ, Pomerance A. Pathology of atrial fibrillation in man. Br Heart J. 1972; 34(5): 520–525, doi: 10.1136/hrt.34.5.520, indexed in Pubmed: 5031645.
27. Kaykha A, Myers J, Desser KB, et al. The prognostic importance of isolated P-wave abnormalities. Clin Cardiol. 2010; 33(6): E87–E93, doi: 10.1002/clc.20628, indexed in Pubmed: 20552614.
28. Hu X, Jiang J, Ma Y, et al. Novel P wave indices to predict atrial fibrillation recurrence after radiofrequency ablation for paroxysmal atrial fibrillation. Med Sci Monit. 2016; 22: 2616–2623, doi: 10.12659/msm.896675, indexed in Pubmed: 27450644.
29. Rao MS. Left atrial volume index (LAVI) in the evaluation of left ventricular diastolic dysfunction. J of Evolution of Med and Dent Sci. 2015; 4(15): 2532–2539, doi: 10.14260/jemds/2015/365.
30. P-wave Terminal Force in Patients With Atrial Fibrillation. (Ptf-AF). https://clinicaltrials.gov/ct2/show/NCT03428971 (December 7, 2019).
31. Benjamin EJ, Chen PS, Bild DE, et al. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. Circulation. 2009; 119(4): 606–618, doi: 10.1161/CIRCULATIONAHA.108.825380, indexed in Pubmed: 19188521.
32. Xiong C, Sonnhag C, Nylander E, et al. Atrial and ventricular function after cardioversion of atrial fibrillation. Br Heart J. 1995; 74(3): 254–260, doi: 10.1136/hrt.74.3.254, indexed in Pubmed: 7547019.
33. Iuchi A, Oki T, Fukuda N, et al. Changes in transmitral and pulmonary venous flow velocity patterns after cardioversion of atrial fibrillation.

American Heart Journal. 1996; 131(2): 270–275, doi: 10.1016/s0002-8703(96)90353-1.
34. Tops LF, Bax JJ, Zeppenfeld K, et al. Effect of radiofrequency catheter ablation for atrial fibrillation on left atrial cavity size. Am J Cardiol. 2006; 97(8): 1220–1222, doi: 10.1016/j.amjcard.2005.11.043, indexed in Pubmed: 16616029.
35. Reant P, Lafitte S, Jaïs P, et al. Reverse remodeling of the left cardiac chambers after catheter ablation after 1 year in a series of patients with isolated atrial fibrillation. Circulation. 2005; 112(19): 2896–2903, doi: 10.1161/CIRCULATIONAHA.104.523928, indexed in Pubmed: 16260634.
36. Song BG, Cho S, Lee S, et al. Atrial mechanical function after maze procedure for atrial fibrillation concomitant with mitral valve surgery. Korean Circ J. 2008; 38(11): 606, doi: 10.4070/kcj.2008.38.11.606.
37. Tsioufis C, Stougiannos P, Taxiarchou E, et al. The interplay between haemodynamic load, brain natriuretic peptide and left atrial size in the early stages of essential hypertension. J Hypertens. 2006; 24(5): 965–972, doi: 10.1097/01.hjh.0000222768.15100.00, indexed in Pubmed: 16612260.
38. Psychari SN, Apostolou TS, Sinos L, et al. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. Am J Cardiol. 2005; 95(6): 764–767, doi: 10.1016/j.amjcard.2004.11.032, indexed in Pubmed: 15757607.
39. Zapolski T, Wysokiński A. Czynność lewego przedsionka u chorych z cukrzycą typu 2. Pol Przegl Kardiol. 2008; 10: 115–121.
40. Salah A, Zhou S, Liu Q, et al. P wave indices to predict atrial fibrillation recurrences post pulmonary vein isolation. Arq Bras Cardiol. 2013; 101(6): 519–527, doi: 10.5935/abc.20130214, indexed in Pubmed: 24173135.