Neuro-Atriomyodegenerative Origin of Atrial Fibrillation and Superimposed Conventional Risk Factors: Continued Search To Configure The Genuine Etiology of "Eternal Arrhythmia"

Petras Stirbys

The Department of Cardiology, Hospital of Lithuanian University of Health Sciences , Kaunas Clinic, Kaunas, Lithuania.

Abstract

Atrial fibrillation (AF) is the most challenging rhythm disturbance worldwide. Arrhythmia and its behavior represent complex pathogenesis highly opposing to contemporary curative modalities. Increasing age of patients carries a certain level of risk for AF. Some underlying diseases in concordance with aging actually accelerate the occurrence of AF. Underestimated superimposed risk factors – aging plus any known risk factor or condition (hypertension, diabetes etc.) – elicit great interest and concern. In light of these concerns we offer an elaborated universal hypothesis in attempt to elucidate the genuine origin of AF substrate. Putative chronic toxicity - toxins and/or involution related pseudo-toxins potentially generate micro- and macro-structural changes in atrial myocardium thus inciting both intracellular damage (degeneration of myocites, apoptosis) and extracellular fibrotic proliferation (interstitial fibrosis, formation of matrices, degeneration of cells with fibrotic replacement). The co-products of related underlying diseases in cooperation with cellular senescence, endogenous overproduction of specific lipids/lipoproteins and other pro-atherosclerotic and/or inflammatory components generate a total atrial response - vascular/microvascular damage, intracellular and extracellular injuries. These organizational arrangements covering the entire atrial myocardium and perhaps ganglionated plexi/autonomic branches of the nervous system eventually cause clinical havoc - atrial overstretch, atrial adaptation/maladaptation, electromechanical dysfunction, arrhythmias, heart failure, etc. In essence, valvular heart disease potentially evokes similar changes "violating" thin atrial walls to obey the same scenario. Depicted atriomyodegenerative processes most likely represent the true nature of AF substrate development. Available clinical and morphological evidence potentially designates the atriomyodegenerative or plausible neuro-atriomyodegenerative origin of AF. Deductively fusion of reasons rather than purely heterogeneity is responsible for AF induction. Thus, the uniform approach and synoptic vision of clinical and pathohistological entity may offer an alternative or refreshed viewpoint in AF substrate formation.

Introduction

Atrial fibrillation (AF) is originally known as a disease of the aging population [1], [2], [3]. Considerable ongoing efforts have been undertaken to identify potential substrates for AF [4]. There has been an explosion in the understanding of the pathophysiology of AF in the last 20 years in particular [5]. Such a traditional introduction of the reports associated with AF becomes encouraging platitude. Unfortunately, our understanding of mechanisms and etiology of AF remains incomplete [5], [6], [7], [8].

In general, it may be postulated that atrial myocardium represents vulnerable tissue, however the primary cause/true nature of nonvalvular AF is still unclear. Van Gelder and colleagues [9] state, that AF is not a benign disease. This disorder apparently is non-autonomous. Mysteries associated with AF are the most pervasive and challenging that remain [10].

Modern AF treatments e.g. ablative procedure, usually do not provide desirable and well-established clinical results; transient effects, high AF recurrence rate or negative side effects are reported [3]. An increasing volume of patients is returning for re-ablation despite years of AF freedom after the procedure [11]. In real life-practice even ultra-radical destructive approach fails to eliminate arrhythmia. Persistent AF recurrences are observed after biatrial surgical ablation procedures with complete isolation of all 4 pulmonary veins under the visual control [12]. Consequently, ablation procedure per se is far from the causal AF treatment.

Despite huge explorative efforts the arrhythmia demonstrates high resistance to contemporary treatment modalities and their notable reluctance to submit to the "domestication". Progressive atriomyodegenerative processes and fibrotic proliferation likelihood opposes to revive still viable atrial myocites and to restore their previous condition. This paper focuses on some aspects associated with arrhythmogenic substrate formation in order to conceptualize the suggested hypothetical scenario. The framework of the new vision is based on brief review of current status of histopathological findings of atrial myocardium and adjacent structures, preferably ganglionated plexi.

Corresponding Author
Petras Stirbys Clinic of Cardiology, Kaunas University of Medicine Hospital, Eiveniu 2, 3007 Kaunas,
Lithuania. pstirbys@kalnieciai.lt

Compact review of histopathological changes in atrial myocardium

Numerous studies have comprehensively analyzed all aspects associated with AF. Therefore we offer just a minimum of the well-known information to present a context for the reader as it relates to the novel hypothetic/speculative postulations.

The progression of AF is caused by the accumulation of damage in cardiomyocites which makes the atria more vulnerable for AF. [3]. Increased fibrosis and inflammatory infiltrates are found in the atria and pulmonary veins-left atrium junctions [8]. Allessie and colleagues [13] have revealed the presence of diffuse biatrial disease in animal models.

Marked histological abnormalities in aging atria were found by Xu and colleagues in their excellent experimental and human studies [4]. They demonstrated abnormal pathohistological and ultrastructural changes - accelerated fibrosis, apoptosis, matrix degeneration and collagen synthesis; the myolysis was documented in aged dogs. Atrial remodeling was characterized by the researchers as "adaptive responses with maladaptive consequences". Degradation of the myofibril structure (myolysis) is found in patients with persistent AF [14], [15] especially during the end-stage of atrial remodeling [16]. Degeneration of myocites with exhibited abundant interstitial fibrosis was also reported by Lee, Kostin, Everett and co-authors [7], [17], [18] it was indicated that structural remodeling may be an adaptive process (dedifferentiation of cardiomyocytes) aimed at protecting the atrial myocites or a maladaptive process (degeneration of cells with fibrotic replacement). Ultrastructural changes - loss of sarcomeres, mitochondrial atrophy, etc. - were documented by electron microscopy [15].

Importantly, cardiac apoptosis results from "mild" but repetitive or prolonged episodes of stress – ischemia, stretch or overload with aging and/or AF [4] chronic hemodynamic overload may be an important factor in triggering a programmed cell death pathway and atrial fibrosis. Due to hemodynamic overload thin atrial walls undergo substantial overstretching [4]. It suggests, that valvular heart disease produces similar atrial effects. According to Zado [19] both AF and heart failure are common conditions and each promotes the other.

Atrial fibrosis in humans may be visualized by newer MRI techniques [20]. Goldberger and co-authors [20] have indicated four stages of atrial fibrosis: no disease, early disease that is not detectable, detectable substrate without AF (ie, preclinical substrate), and manifest AF. The first three stages likely represent an atrial adaptation period while the last one represents – disadaptation. Noteworthy to stress, that in animal models reversal or prevention of fibrosis prevents AF [21], [22].

Superimposed risk factors - a set of circumstances initiating AF

Various reports have highlighted the role of common risk/proarrhythmic factors and predisposing conditions which contribute to the development of AF: old age, ischemic heart disease, rheumatic, valvular, thyroid disease, pre-existent pulmonary disease, hypertension, heart failure, renal failure, chronic hemodynamic overload, obesity, cardiac lipid everload, dyslipidemia, diabetes, metabolic syndrome, high body mass index, obstructive sleep apnea, hypoxia, cardiomyopathy, sick sinus syndrome, significant alcohol/tobacco use or abuse, inflammation, interstitial fibrosis, atrial overstretch, atrial

volumetric changes, oxidative stress and prolonged PR interval [6], [23]-[27]. Some of them are attributed to powerful category. Recently underweight was indicated as a risk factor as well [28]. Atriomyopathy or fibrotic atrial cardiomyopathy is also a favorable milieu for AF [20], [29]. Interactions between these risk factors or their cumulative effects may not be excluded.

AF is strongly age-dependent with approximately 70% of the AF patients between 65 and 85 years [30]. The incidence increases markedly with advancing age [31]. As the population ages, AF will become more and more prevalent [32]. Let's assume that aging is the most important and the most prevalent risk factor for AF. The other well-known proarrhythmic factors however may act in solidarity with the age-dependent one or in self-independent manner as alone contributor. In AF patients the hypertension and high body mass index are likely to increase left ventricular stiffness by elevating vascular resistance, thereby leading to increased left atrial enlargement [7]. Herein two overlapping risk factors for AF are mentioned, i.e., hypertension and high body mass index. Individual advanced age as the 3rd factor is to be kept in mind. Due to the convergence of several risks the atrial myocardium becomes much more vulnerable. The preferred aging risk factor in some cases (e.g., in valvular heart disease) may play a less important role, however not of a zero value.

Notably, left atrium size is increased in elderly patients [37] not just in patients suffering from valvular heart disease. Consequently clear relationship may be tracked: an obvious link exists between nonvalvular AF, valvular AF, heart failure, atrial overstretch, atrial volumetric overload, e.g. due to mitral regurgitation and/or due to atrial overload on aging or on congestive heart failure basis. It means that sensitive atrial myocites and the entire atrial myocardium are easily vulnerable. Obviously, atrial enlargement per se is a favorable pro-arrhythmic parameter.

In the natural course of heart failure progression, the viable myocardium is gradually replaced by collagen-rich tissue [33]. It is noteworthy that the progression of heart failure or any other underlying disorder takes time; concordantly the patients are growing older thereby complicating the course of the corresponding chronic disease. Ischemic heart disease, diabetes, obesity, metabolic disorders, chronic obstructive pulmonary disease, inflammation and much more negative ingredients solitary or by coalescence favor AF induction. Co-existence of superimposed factors is to be considered as synoptic heterogeneity of causes which serve for the formation of arrhythmogenic substrate.

Age-related involution processes taking part in the entire human body and atrial wall are actually accelerated by underlying diseases or by appropriate comorbidity. Reportedly, abnormal lipid accumulation is observed in the cardiomyocytes of obese and diabetic patients and is thought to contribute to an increased risk of arrhythmia [27]. Overall acceleration of activity of factors mentioned results in the transition of paroxysmal to long-standing AF and finally to atrial functional abnormality.

It seems unbelievable that the underlying heart/non-heart disease may form circumscribed region(s) as a substrate for AF and that these limited pathological areas might be abolished by ablative or other destructive intervention [34]; alternative pathophysiology of AF may be depicted as an appearance of focal area (e.g. inflammation) which expands centrifugally to the reminder of the atria. A similar mechanism is described of focal atrial tachycardia after surgery [34].

Hypothetic, near-realistic considerations

It is most likely that the AF occurrence is time-dependant and it correlates with the coincident phase of advanced underlying disease which in turn produces unfavorable "environmental" pro-atrial toxins.

Two hypothetic constituent components participating in the primary substrate formation may be suggested: 1) toxic and 2) pseudo-toxic containing pro-degenerative and pro-arrhythmic ingredients. The first one is represented by the underlying etiology which does not directly pertain to atria. It may be renal failure, rheumatic disease along with its inflammation ingredient and corresponding consequences which in turn leads to valvular incompetence, atrial overload, overstretch, enlargement and evolving rough structural changes. The same can be said about the adverse synergistic effects on atrial myocardium that appear on the basis of above mentioned wide spectrum of various underlying diseases. The nature of these toxic products is to be proven yet however they demonstrate "natural" affinity for atrial myocites.

Pseudo-toxic initiating mechanism may occur due to the complex involution/regressive alterations in the entire human body associated with aging processes. Cellular senescence, endogenous overproduction of specific lipids/lipoproteins [35], [36] and other pro-atherosclerotic components sooner or later do evoke vascular/microvascular damage resulting in intracellular and extracellular injury. In this regard the coronary artery disease may play the crucial role. Hypertension and diabetes may also be included into the list of pro-pseudo-toxic activities. Most likely atria are affected negatively by both factors – toxic and pseudo-toxic which finally are responsible for the release of extraordinarily complex atriomyodegenerative or neuro-atriomyodegenerative pathology. These putative key factors likely determine the creation of genuine pathophysiological substrate for arrhythmia. Thus, atrial myocardium is compromised as a target organ for the activity of co-products of underlying disease(s)/conditions. In this regard the underlying diseases apparently trigger the whole clinical entity associated with AF. Atrial propensity to atract the provocative factors delegated by underlying or comorbid illnesses might be the target of future investigation.

Individual peculiarities (atrial vulnerability, susceptibility, comorbidity, immunological state etc.) negatively contribute to AF substrate formation and exacerbation of AF attacks. Elderly patients being free from AF probably are immune to provocative risks; some of them, especially those with the genetic robustness are refractory to arrhythmias throughout the life span.

Some authors indicate that AF manifests itself as a result of multiple heterogeneous groups of disorders [6]. According to Takemoto et al. [38] AF starts as paroxysmal but can evolve relentlessly to the persistent and permanent forms; the mechanisms governing such a transition are unknown. It is considered that the AF itself is not causal. However, it has been demonstrated that AF itself may result in changes in electrophysiology that promote further AF – so-called "AF begets AF" [39].

The role of ganglionated plexi

It is well known that the autonomic nervous system (ANS) is involved in the onset of AF [40]. Cardiac ANS system consists of extrinsic and intrinsic components, which play significant role in the modulation of the cardiac function [40]. This system has great plasticity in the initiation and maintenance of AF [41]-[43]. Intrinsic cardiac neurons are found in the atria and are innervated with both sympathetic and parasympathetic neurons that are connected to both

the spinal cord and medullary neurons [44]. According to Kondo et al. [45] ganglionated plexi are highly associated with AF and are key targets for a maze procedure. Some reports show that intrinsic nerve activity could influence the occurrence of atrial triggers that would increase atrial vulnerability to AF [46]. Shen and colleagues [47] have stressed that activity of ANS is crucial in triggering paroxysmal AF. Interestingly, atrial neural network was described recently [48], [49].

Heightened atrial sympathetic innervation has been demonstrated in patients with persistent AF [50]. Relative curative influence on AF by generalized denervation of atria is reported [46], [51]. While targeting autonomic cardiac ganglia alone does not prevent long-term AF recurrences [52]. Some observations show that ganglionated plexi ablation without pulmonary veins' isolation may be proarrhythmic with decreased atrial sympathetic and parasympathetic innervations [53].

Apparently the ANS contribute to the electrophysiological creation of substrate for AF. Direct autonomic nerve recordings demonstrate that simultaneous sympathovagal discharges and intrinsic cardiac nerve activities are common triggers of AF [47]. We are still unaware as to which risk factor(s) predispose the activation of ganglionated plexi to initiate and/or to maintain AF. These factors are perhaps already known risks, i.e. the common conditions that were enumerated above (aging, hypertension, diabetes and so forth). Noteworthy, ganglionated plexi could self-activate the influence of extrinsic cardiac ANS [54]. Xi and Cheng [55] have postulated that namely dysfunction of ANS impacts the pathogenesis of AF. Again, the dysfunction or imbalance of ANS perhaps stems from the hierarchic centers residing in spinal cord or in medulla. Such an uncertainty generates the idea of degenerative origin of ANS preferably its parasympathetic branch, thus allowing to be outweighed by sympathetic one. The question is: when and why the activity of ANS is accelerated and why this activity is depressed before the onset of AF? Asymmetry in activities of sympathetic and parasympathetic branches of ANS may explain the dominance of sympathetic component. Recently experimental studies have shown neural remodeling with atrial nerve sprouting and sympathetic hyperinnervation in metabolic syndrome [56]. Ablation impacts favorably the overall success by neutralizing the activity of both branches of ANS. In such a manner the discordance of ANS activity is annihilated presumably.

The degenerative predilection of ganglionated plexi is to be validated. Unfortunately conclusive data of microscopic changes of ganglionated plexi pertaining to AF are lacking. The epicardial fat pad most likely undergoes mechanical over tension, dilation and expansion which are associated with volumetric changes of atria. According to the report of Maesen and co-authors [57] left atrial epicardial adipose tissue (peri-atrial fat) increase with left atrial volume. Thus, secondary changes might be inspired and conspired, at least theoretically, with the involvement of peri/epicardial autonomous neural network.

The role of putative abnormal sympathetic and/or parasympathetic contribution to support the AF substrate formation is to be established yet. Nevertheless, the term of "neuro-degenerative" was incorporated prematurely into the title of this article. The neuro-degenerative component is probably activated due to atrial enlargement especially when it reaches critical parameters. At least theoretically the neuro-degenerative ingredient may play specific role in terms of maintaining rather than initiating of AF.

Unlearned but helpful definitions

In general, some nosological diseases do not demonstrate a complete set of classical symptoms. The term "forme fruste" represents an atypical or attenuated manifestation of a disease with the implications of incompleteness, partial presence or aborted state. There is a suspicion that overall ischemic heart disease, rheumatic disease, hypertension, diabetes, obesity etc., are not full-blown while lacking of AF. Arrhythmia potentially emerges as a natural course with constituted components of chronic diseases mentioned at least at their end-stage. The increasing age of the patient favorably accelerates the formation of AF substrate. In other words, aging as a "confident" ally strongly supports the release of AF. All together, a pro-arrhythmic underlying disease, AF per se, along with the patient's disposing age leads gradually to the "forme pleine" condition, i.e., to accomplished form of the disease. Myocardial devastation as a fait accompli reflects the presence of continuous pathognomonic sign of the provocative diseases. Such predisposing conditions or etiological heterogeneity most likely beget AF, not "AF begets AF". The onset of AF actually depends on the degree of atrial involvement into the developing processes.

Conclusion

We would like to conjoin multifactorial/multisource etiology into a unique monoetiologic concept of arrhythmogenesis. The proposed hypothesis is focused on conceptualization of the neuro-atriomyodegenerative processes which likely occur due to various launching/predegenerative factors of underlying diseases that initiate not only AF, but anatrial remodeling phenomenon as well. Single action or coaction of several prodegenerative ingredients potentially leads to a myodegenerative endpoint at the atrial level. A fusion of reasons rather than purely heterogeneity is most likely responsible for AF induction.

Atrial myocardium might be treated as an exclusive/specific milieu accumulating provocative troublemakers delegated from extracardiac or intracardiac sources along with the favorable proactivity of aging component. Thus, cooperative reasons – toxins and/or pseudo-toxins potentially affect the atrial myocardium and are responsible for AF. The possibility of interaction between these factors cannot be ruled out. Deductively, it may be postulated that AF is not an autonomous disease. In fact, atrial myocardium represents the "true victim" of superimposed invaders – toxic and pseudo-toxic products stemming from various chronic diseases or conditions. Hence, atrial myocardium undergoes violation by harmful co-products finally resulting in atrial remodeling. This abnormality is highly resistant to traditional AF therapies. Any well-known progressive degenerative disorder (e.g., idiopathic, arrhythmogenic, dilatative cardiomyopathy, degenerative valve, joint disease, neurodegenerative diseases etc.), are hardly reversible and usually are refractory to medical control. In other words, intramural deconstruction or reverse of already precipitated excessive fibrotic changes is hardly feasible. Such an image of arrhythmogenesis fundamentally reveals our failing efforts to restore the previous viability of affected myocites especially when degenerative processes continue their activity.

Some uncertainty emerges as far as whether the targeted ablation of viable myocites is helpful or not to regain the previous atrial functional status. To revive and to maintain the inherent viability of myocites, not to destroy them (e.g., by ablation) potentially would be the best choice of cure. Theoretically the annihilation of unfavorable intracellular changes or extracellular matrices might be more beneficial rather than execution of cardiac cells. Huge efforts are to be invested into the novel and more effective treatment modalities precluding and eliminating odds for AF. If neuro-atriomyodegenertive origin of AF is recognized the new treatment strategies should be established.

Thus, the prevention of underlying diseases, effective neuro-myoprotective therapy and hampering measures against aging might be the best strategy for AF prevention. Interestingly, weight loss results in regress of AF from persistent to paroxysmal [58]. Widely declared upstream AF control [59], [60] might be interpreted as a preventive "golden approach" not allowing the pathology to descent into the preclinical and/or clinical phases. Thus, underlying disease must be carefully identified and proeperly managed. All the remaining treatment options (pharmacological, non-pharmacological, cardioversion, ablation therapy etc.) actually represent palliation rather than eradication of „eternal arrhythmia". Aging protection and involution mitigation measures are to be invented as well.

Finally, the synthesis of well-known risk factors by unifying their features potentially enables to state/hypothesize that atrial myocardium demonstrantes high affinity and sensitive effects for specific toxins (unidentified yet) or pseudo-toxins in a „suicide manner" . The value of synoptic toxicity-induced model of AF development remains to be debated.

References

1. Wilke Thomas, Groth Antje, Mueller Sabrina, Pfannkuche Matthias, Verheyen Frank, Linder Roland, Maywald Ulf, Bauersachs Rupert, Breithardt Günter. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace. 2013;15 (4):486–93.

2. Krijthe Bouwe P, Kunst Anton, Benjamin Emelia J, Lip Gregory Y H, Franco Oscar H, Hofman Albert, Witteman Jacqueline C M, Stricker Bruno H, Heeringa Jan. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur. Heart J. 2013;34 (35):2746–51.

3. van Marion MSc Denise M S, Lanters MdEva A H, Wiersma MScMarit, Allessie Md PhDMaurits A, Brundel PhDBianca B J J M, de Groot Md PhDNatasja M S. Diagnosis and Therapy of Atrial Fibrillation: The Past, The Present and The Future. J Atr Fibrillation. 2015;8 (2):–.

4. Xu Guo-Jun, Gan Tian-Yi, Tang Bao-Peng, Chen Zu-Heng, Mahemuti Ailiman, Jiang Tao, Song Jian-Guo, Guo Xia, Li Yao-Dong, Miao Hai-Jun, Zhou Xian-Hui, Zhang Yu, Li Jin-Xin. Accelerated fibrosis and apoptosis with ageing and in atrial fibrillation: Adaptive responses with maladaptive consequences. Exp Ther Med. 2013;5 (3):723–729..

5. Wyse D George, Van Gelder Isabelle C, Ellinor Patrick T, Go Alan S, Kalman Jonathan M, Narayan Sanjiv M, Nattel Stanley, Schotten Ulrich, Rienstra Michiel. Lone atrial fibrillation: does it exist?. J. Am. Coll. Cardiol. 2014;63 (17):1715–23.

6. Woods Christopher E, Olgin Jeffrey. Atrial fibrillation therapy now and in the future: drugs, biologicals, and ablation. Circ. Res. 2014;114 (9):1532–46.

7. Lee Jung Myung, Lee Hancheol, Janardhan Ajit H, Park Junbeom, Joung Boyoung, Pak Hui-Nam, Lee Moon-Hyoung, Kim Sung Soon, Hwang Hye Jin. Prolonged atrial refractoriness predicts the onset of atrial fibrillation: A 12-year follow-up study. Heart Rhythm. 2016;13 (8):1575–80.

8. Nguyen Bich Lien, Fishbein Michael C, Chen Lan S, Chen Peng-Sheng, Masroor Saqib. Histopathological substrate for chronic atrial fibrillation in humans. Heart Rhythm. 2009;6 (4):454–60.

9. Van Gelder I C, Smit M D, Alings M, Crijns H J G M. Upstream therapy in patients with early atrial fibrillation: The relevance of the Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure

(RACE 3) study. Neth Heart J. 2010;18 (11):522–3.

10. Wyndham C R. Atrial fibrillation: the most common arrhythmia. Tex Heart Inst J. 2000;27 (3):257–67.

11. Y Shah, MFerrara, EHansinger, DLMusat, MWPreminger. Re-ablation procedural findings and clinical outcomes in patients with very late recurrence after initially successful ablation of atrial fibrillation (Abstr.). Heart Rhythm. 2016. 2006;0:469–0.

12. Takahashi Kenta, MiyauchiYasushi, HayashiMeiso, IwasakiYu-Ki, YodogawaKenji, TsuboiIppei, HayashiHiroshi, OkaEiichiro, Ito HagiwaraKanako, FujimotoYuhi, ShimizuWataru. Mechanisms of postoperative atrial tachycardia following biatrial surgical ablation of atrial fibrillation in relation to the surgical lesion sets. Heart Rhythm. 2016;13 (5):1059–65.

13. Allessie M A, BonkeF I, SchopmanF J. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ. Res. 1977;41 (1):9–18.

14. Brundel Bianca J J M, AusmaJannie, van GelderIsabelle C, Van der WantJohan J L, van GilstWiek H, CrijnsHarry J G M, HenningRobert H. Activation of proteolysis by calpains and structural changes in human paroxysmal and persistent atrial fibrillation. Cardiovasc. Res. 2002;54 (2):380–9.

15. Thijssen V L, AusmaJ, BorgersM. Structural remodelling during chronic atrial fibrillation: act of programmed cell survival. Cardiovasc. Res. 2001;52 (1):14–24.

16. Brundel Bianca J J M, KeLei, DijkhuisAnne-Jan, QiXiaoYan, Shiroshita-TakeshitaAkiko, NattelStanley, HenningRobert H, KampingaHarm H. Heat shock proteins as molecular targets for intervention in atrial fibrillation. Cardiovasc. Res. 2008;78 (3):422–8.

17. S Kostin, GKlein, ZSzalay, SHein, EPBauer, JSchaper. Sructural correlate of atrial fibrillation in human patients. Cardiovasc Res. 2002; 54:361-379. View Article: Google Scholar. 2015;0:0–0.

18. Everett Thomas H, WilsonEmily E, VerheuleSander, GuerraJose M, ForemanScott, OlginJeffrey E. Structural atrial remodeling alters the substrate and spatiotemporal organization of atrial fibrillation: a comparison in canine models of structural and electrical atrial remodeling. Am. J. Physiol. Heart Circ. Physiol. 2006;291 (6):H2911–23.

19. ES Zado. EP news: allied professionals. Heart Rhythm. 2016. 2016;13:0–0.

20. Goldberger Jeffrey J, AroraRishi, GreenDavid, GreenlandPhilip, LeeDaniel C, Lloyd-JonesDonald M, MarklMichael, NgJason, ShahSanjiv J. Evaluating the Atrial Myopathy Underlying Atrial Fibrillation: Identifying the Arrhythmogenic and Thrombogenic Substrate. Circulation. 2015;132 (4):278–91.

21. Lee Ken W, EverettThomas H, RahmutulaDulkon, GuerraJose M, WilsonEmily, DingChunhua, OlginJeffrey E. Pirfenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. Circulation. 2006;114 (16):1703–12.

22. Shi Yanfen, LiDanshi, TardifJean-Claude, NattelStanley. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. Cardiovasc. Res. 2002;54 (2):456–61.

23. AJ Camm, PKirchhof, GYLip, USchotten, ISavelieva, SErnst. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010. 2010;0:0–0.

24. Magnani Jared W, RienstraMichiel, LinHonghuang, SinnerMoritz F, LubitzSteven A, McManusDavid D, DupuisJosée, EllinorPatrick T, BenjaminEmelia J. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. Circulation. 2011;124 (18):1982–93.

25. Schnabel Renate B, SullivanLisa M, LevyDaniel, PencinaMichael J, MassaroJoseph M, D'AgostinoRalph B, Newton-ChehChristopher, YamamotoJennifer F, MagnaniJared W, TadrosThomas M, KannelWilliam B, WangThomas J, EllinorPatrick T, WolfPhilip A, VasanRamachandran S, BenjaminEmelia J.

Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009;373 (9665):739–45.

26. Youn Ji-Youn, ZhangJun, ZhangYixuan, ChenHouzao, LiuDepei, PingPeipei, WeissJames N, CaiHua. Oxidative stress in atrial fibrillation: an emerging role of NADPH oxidase. J. Mol. Cell. Cardiol. 2013;62 ():72–9.

27. Joseph Leroy C, SubramanyamPrakash, RadliczChristopher, TrentChad M, IyerVivek, ColecraftHenry M, MorrowJohn P. Mitochondrial oxidative stress during cardiac lipid overload causes intracellular calcium leak and arrhythmia. Heart Rhythm. 2016;13 (8):1699–706.

28. W-H Lim, E-KChoi, S-HKang, S-RLee, K-DHan. Underweight is a risk factor for atrial fibrillation: a nationwide population-based study (Abstr.). Heart Rhythm. 2016. 2016;13:0–0.

29. Kottkamp Hans. Atrial fibrillation substrate: the "unknown species"-- from lone atrial fibrillation to fibrotic atrial cardiomyopathy. Heart Rhythm. 2012;9 (4):481–2.

30. V Fruster, LERyden, DSCannom. ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology Foundation/American heart Association Task Force on Practice Guidelines. Circulation. 2011. 2011;57:101–198.

31. Chatap Guy, GiraudKarine, VincentJean-Pierre. Atrial fibrillation in the elderly: facts and management. Drugs Aging. 2002;19 (11):819–46.

32. Houck Charlotte A, TeuwenChristophe P, BogersAd J J C, de GrootNatasja M S. Atrial tachyarrhythmias after atrial switch operation for transposition of the great arteries: Treating old surgery with new catheters. Heart Rhythm. 2016;13 (8):1731–8.

33. Sokal Adam, LenarczykRadoslaw, KowalskiOskar, MitregaKatarzyna, PlutaSlawomir, Stabryla-DeskaJoanna, StrebWitold, UrbanikZofia, KrzeminskiTadeusz F, KalarusZbigniew. Prognostic value of collagen turnover biomarkers in cardiac resynchronization therapy: A subanalysis of the TRUST CRT randomized trial population. Heart Rhythm. 2016;13 (5):1088–95.

34. de Groot Natasja M S, ZeppenfeldKatja, WijffelsMaurits C, ChanWing King, BlomNico A, Van der WallErnst E, SchalijMartin J. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. Heart Rhythm. 2006;3 (5):526–35.

35. Veronica Guarner, EstherRubio-Ruiz Maria. Aging, metabolic syndrome and the heart. Aging Dis. 2012;3 (3):269–79.

36. Wessely Rainer. Atherosclerosis and cell cycle: put the brakes on! Critical role for cyclin-dependent kinase inhibitors. J. Am. Coll. Cardiol. 2010;55 (20):2269–71.

37. Nikitin N P, WitteK K A, ThackrayS D R, GoodgeL J, ClarkA L, ClelandJ G F. Effect of age and sex on left atrial morphology and function. Eur J Echocardiogr. 2003;4 (1):36–42.

38. Takemoto Yoshio, RamirezRafael J, YokokawaMiki, KaurKuljeet, Ponce-BalbuenaDaniela, SinnoMohamad C, WillisB Cicero, GhanbariHamid, EnnisSteven R, Guerrero-SernaGuadalupe, HenziBettina C, LatchamsettyRakesh, Ramos-MondragonRoberto, MusaHassan, MartinsRaphael P, PanditSandeep V, NoujaimSami F, CrawfordThomas, JongnarangsinKrit, PelosiFrank, BogunFrank, ChughAman, BerenfeldOmer, MoradyFred, OralHakan, JalifeJosé. Galectin-3 Regulates Atrial Fibrillation Remodeling and Predicts Catheter Ablation Outcomes. JACC Basic Transl Sci. 2016;1 (3):143–154.

39. Wijffels M C, KirchhofC J, DorlandR, AllessieM A. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92 (7):1954–68.

40. Miyazaki Shinsuke, NakamuraHiroaki, TaniguchiHiroshi, HachiyaHitoshi, IchiharaNoboru, TakagiTakamitsu, IwasawaJin, KuroiAkio, WatanabeTomonori, HiraoKenzo, IesakaYoshito. Impact of the order of the targeted pulmonary vein on the vagal response during second-generation cryoballoon ablation. Heart Rhythm.

2016;13 (5):1010–7.

41. Yuan B X, ArdellJ L, HopkinsD A, LosierA M, ArmourJ A. Gross and microscopic anatomy of the canine intrinsic cardiac nervous system. Anat. Rec. 1994;239 (1):75–87.

42. Scherlag Benjamin J, NakagawaHiroshi, JackmanWarren M, YamanashiWilliam S, PattersonEugene, PoSunny, LazzaraRalph. Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. J Interv Card Electrophysiol. 2005;13 Suppl 1 ():37–42.

43. Po Sunny S, NakagawaHiroshi, JackmanWarren M. Localization of left atrial ganglionated plexi in patients with atrial fibrillation. J. Cardiovasc. Electrophysiol. 2009;20 (10):1186–9.

44. Potential clinical relevance of the "little brain" on the mammalian heart. Exp Physiol. 2008. 2008;93:165–176.

45. Identification of left atrial ganglionated plexi by dense epicardial mapping as ablation targets for the treatment of concomitanat atrial fibrillation. Pacing Clin Electrophysiol. 2013. 2013;36:1336–1341.

46. Ganglionated plexi and ligament of Marshall ablation reduces atrial vulnerability and causes stellate ganglion remodeling in ambulatory dogs (Abstr.). Heart Rhythm. 2016. 2016;13:2083–2060.

47. Shen Mark J, ChoiEue-Keun, TanAlex Y, LinShien-Fong, FishbeinMichael C, ChenLan S, ChenPeng-Sheng. Neural mechanisms of atrial arrhythmias. Nat Rev Cardiol. 2011;9 (1):30–9.

48. Hou Yinglong, ScherlagBenjamin J, LinJiaxiong, ZhouJing, SongJianguo, ZhangYing, PattersonEugene, LazzaraRalph, JackmanWarren M, PoSunny S. Interactive atrial neural network: Determining the connections between ganglionated plexi. Heart Rhythm. 2007;4 (1):56–63.

49. Lin Jiaxiong, ScherlagBenjamin J, NiuGuodong, LuZhibing, PattersonEugene, LiuShaowen, LazzaraRalph, JackmanWarren M, PoSunny S. Autonomic elements within the ligament of Marshall and inferior left ganglionated plexus mediate functions of the atrial neural network. J. Cardiovasc. Electrophysiol. 2009;20 (3):318–24.

50. Evidence for increased atrial sympathetic innervations in persistent human atrial fibrillation. Pacing Clin Electrophysiol. 2006. 2006;0:821–829.

51. Recent insights into the role of the autonomic nervous system in the creation of substrate for atrial fibrillation. Implications for therapies targeting the atrial autonomous nervous system. Circ Arrhythm Electrophysiol. 2012. 2012;0:850–859.

52. Vagal denervation and atrial fibrillation inducibility : epicardial fat pad ablation does not have long-term effects. Heart Rhythm. 2006. 2006;0:701–708.

53. Mao Jun, YinXiandong, ZhangYing, YanQian, DongJianzeng, MaChangsheng, LiuXingpeng. Ablation of epicardial ganglionated plexi increases atrial vulnerability to arrhythmias in dogs. Circ Arrhythm Electrophysiol. 2014;7 (4):711–7.

54. Is the atrial neural plexis a therapeutic target in atrial fibrillation?. Methodist Debakey Cardiovasc J. 2015. 2015;0:82–86.

55. Xi Yutao, ChengJie. Dysfunction of the autonomic nervous system in atrial fibrillation. J Thorac Dis. 2015;7 (2):193–8.

56. Nerve sprouting, sympathetic hyperinnervation and increased vulnerability of atrial fibrillation in a porcine model of metabolic syndrome (Abstr.). Heart Rhythm. 2016. 2016;13:54–0.

57. Peri-atrial fat is not predictive of outcome in hybrid atrial fibrillation (Abstr.). Heart Rhythm. 2016. 2016;13:303–0.

58. Prevention and regressive effect of weight loss and risk factor modification on atrial fibrillation (Reverse-AF) (Abstr.). Heart Rhythm. 2016. 2016;13:49–0.

59. Van Gelder I C, SmitM D, AlingsM, CrijnsH J G M. Upstream therapy in patients with early atrial fibrillation: The relevance of the Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study. Neth Heart J. 2010;18 (11):522–3.

60. Qi Wen-Wei, LiuTong, XuGang, LiLi-Feng, LiangYing-Zi, YeLan, LiGuang-Ping. Upstream therapeutic strategies of Valsartan and Fluvastatin on Hypertensive patients with non-permanent Atrial Fibrillation (VF-HT-AF): study protocol for a randomized controlled trial. Trials. 2015;16 ():–.