Heart Failure and Atrial Fibrillation: From Basic Science to Clinical Practice

João Pedro Ferreira 1,2,* and Mário Santos 2,3

1 Internal Medicine Department, Centro Hospitalar do Porto, Porto 4099-001, Portugal

2 Department of Physiology and Cardiothoracic Surgery, Cardiovascular Research and Development Unit, Faculty of Medicine, University of Porto, Porto 4200-319, Portugal; E-Mail: mariossantos001@gmail.com

3 Cardiology Department, Centro Hospitalar do Porto, Porto 4099-001, Portugal

* Author to whom correspondence should be addressed; E-Mail: u10161@chporto.min-saude.pt; Tel.: +351-22-207-75-00; Fax: +351-22-205-32-18.

Academic Editor: Yi-Han Chen

Received: 29 November 2014 / Accepted: 27 January 2015 / Published: 30 January 2015

Abstract: Heart failure (HF) and atrial fibrillation (AF) are two growing epidemics associated with significant morbidity and mortality. They often coexist due to common risk factors and shared pathophysiological mechanisms. Patients presenting with both HF and AF have a worse prognosis and present a particular therapeutic challenge to clinicians. This review aims to appraise the common pathophysiological background, as well as the prognostic and therapeutic implications of coexistent HF and AF.

Keywords: atrial fibrillation (AF); heart failure (HF); pathophysiology

1. Introduction

In developed countries, heart failure (HF) affects 2% to 3% of the population and is a major cause of morbidity and mortality [1]. Despite the therapeutic progress observed in past decades, the prognosis of HF patients remains poor [2]. Atrial fibrillation (AF) is the most common heart rhythm disorder with an overall prevalence of 1% [3]. Similarly to HF, it is also associated with significant morbidity, mortality and an economic burden [4]. These two diseases often coexist because they share common risk factors (older age, hypertension, diabetes mellitus, valvular and ischemic heart disease) and pathophysiological
mechanisms. In addition, they can promote each other by inducing neuro-hormonal, electrophysiological and hemodynamic changes. Notably, the development of the second is associated with a worse prognosis regardless of which condition comes first [5]. There are several specific therapeutic implications to each disease when they coexist.

This review aims to appraise the common pathophysiological background, as well as the prognostic and therapeutic implications of coexistent HF and AF.

2. Combined Heart Failure and Atrial Fibrillation: Epidemiological and Prognostic Implications

Among HF trials and registries, the prevalence of AF ranged from 13% to 41%, depending in part upon age and the severity of HF [5,6], with no differences between heart failure with preserved or reduced ejection [7]. Conversely, the prevalence of HF in recent trials involving AF patients varied from 30% to 65% [8,9]. In reference to their temporal relationship, Framingham cohort study [5] showed that the frequency of HF preceding AF was similar to AF preceding HF.

The prognostic importance of the presence of AF in HF patients is well established in different settings. Both observational studies [5] and randomized clinical trials [6,10] showed that the presence of AF was associated with increased hospitalization, hospital stay and mortality of HF patients. A recent meta-analysis that included more than 30,000 HF patients showed that those with AF had a 33% increase in mortality [11].

Together, these data show that HF and AF often coexist and when together they are associated with worse prognosis.

3. Common Pathophysiological Background for Heart Failure and Atrial Fibrillation

3.1. Hemodynamic Mechanisms

An increased left ventricular filling pressure (LVFP) is a hallmark feature of the HF hemodynamic profile, which can be caused by either a systolic or diastolic dysfunction [1]. This increased LVFP is transmitted to the left atrium, which will lead to several macro- and microscopic changes in this chamber. The elevated atrial pressure is further increased when functional mitral regurgitation develops along the LV remodeling. This increased stress in the atrium wall is mechanotransduced and will drive several of the cellular and molecular mechanisms discussed below.

On the other side, AF can interfere with the ability of the heart to pump or accommodate blood. An increased resting heart rate and an exaggerated heart rate response to exercise shorten the LV filling time. Together with the concomitant loss of an effective atrial contraction, AF can significantly compromise diastolic function. In addition, a sustained rapid heart rate can impair systolic function by reducing myocardial contractility [12] (Table 1 and Figure 1).
Table 1. Common pathophysiologic mechanisms of heart failure and atrial fibrillation.

| Items          | Pathophysiologic Mechanisms                                      |
|----------------|------------------------------------------------------------------|
| Hemodynamic    | Increased left ventricle filling pressure                         |
|                | Increased resting heart rate                                     |
|                | Exaggerated heart rate response to exercise                      |
|                | Loss of atrial contraction                                       |
|                | Reduced myocardial contractility                                  |
| Neuro-hormonal | Renin-angiotensin-aldosterone system activation                   |
|                | Adrenergic activation                                             |
|                | Increase of transforming growth factor-β1                       |
| Cellular       | Extracellular matrix alteration                                   |
|                | Intracellular calcium overload                                    |

Figure 1. Common pathophysiologic background for heart failure (HF) and atrial fibrillation (AF). LA: left atrial.

3.2. Neuro-Hormonal Mechanisms

Atrial stretch results in an increased neurohormonal activation. The renin-angiotensin-aldosterone system (RAAS) activation enhances signal transduction of downstream pathways such as mitogen-activated protein kinase (MAPK) [13–15], Janus kinase (JAK)/signal transducers and activators of transcription (STAT) [15], transforming growth factor-β1 (TGF-β1) [16,17], and angiotensin II activated platelet-derived growth factor-A (PDGF-A) pathways [18], which play an important role in fibrosis formation and cardiac remodeling. Additionally, increased levels of Rac1—a small guanosine triphosphate-binding
protein, and nuclear factor-kappa B (NF-κB)—a transcription factor, are increased in AF tissues [19,20]. Rac1 may itself activate NF-κB [21] and STAT [22], and angiotensin II can activate all these signaling pathways [23]. Activation of angiotensin II type 1 (AT-1) receptors initiates a cascade of phosphorylation processes that activate a family of mitogen-activated protein kinases (MAP kinases) that promote atrial hypertrophy, fibrosis, and apoptosis, contributing to the structural remodeling of this heart chamber [24]. The stimulation of AT-1 receptors also activates phospholipase C leading to inositol-1,4,5-triphosphate (IP3) that mediates the release of calcium from the sarcoplasmic reticulum which can have pro-fibrotic and arrhythmogenic effects [25]. Enhanced left ventricular wall stress also increases neurohormonal activation resulting in myocardial hypertrophy [26] and interstitial remodeling [27]. Transforming growth factor β1 is involved in maladaptive remodeling [28] and insulin-like growth factor 1 results in adaptive remodeling [29]. Matrix metalloproteinases that degrade extracellular matrix proteins can increase ventricular remodeling in HF. Adrenergic activation, an important feature of HF [30] may also be impact on AF pathophysiology. There are multiple lines of evidence linking high levels of β1-adrenergic signaling, as predicted for β1 389-arginine homozygotes, to the development of AF [31]. Higher adrenergic activity has been shown to increase the inducibility of AF in a dose-dependent manner [32,33]. Furthermore, in isolated human right atrial preparations, isoproterenol infusion has been shown to increase the frequency of atrial early and delayed after-depolarizations, phenomena that have been implicated in initiating AF [34] (Table 1 and Figure 1).

3.3. Cellular and Intra-Cellular Mechanisms

In the interstitial compartment, fibroblasts modify the extracellular matrix with effects on ventricular size, structure, and stiffness. If AF persists, further structural changes occur, promoting volume increase of atrial myocytes, sarcomeres misalignment, accumulation of glycogen, and gap-junctional remodeling [35]. In the presence of HF, the auricular stretch induced by volume overload largely contributes to AF pathophysiology [36]. Furthermore, HF can cause atrial dilatation that serve as a mold able to support a large number of re-entry wavelets that are essential for AF maintenance [7]. In synthesis, HF creates a favorable structural background for atrial re-entry and ectopic activity [7], promoting further arrhythmogenesis [37].

Calcium overload of atrial myocytes occurs early in the development of AF and causes changes in gene expression that down-regulate the L-type calcium current, leading to atrial refractory period shortening in order to compensate for the calcium overload and consequently promoting multiple re-entry [38]. After depolarization, sarcoplasmic calcium is recaptured to the sarcoplasmic reticulum via the calcium ATPase (SERCA2a). In HF, SERCA2a is reduced leading to high cytosolic and low sarcoplasmic reticulum calcium concentrations [39]. Atrial fibrillation itself activates stretch-mediated channels that enhance calcium binding to cellular myofilaments that, in turn, can produce delayed after-depolarisations and triggered activity. Persistent and paroxysmal AF are associated with profound impairment in calcium metabolism [40–42]. Increased diastolic sarcoplasmic reticulum calcium leak and related delayed after-depolarizations/triggered activity promote cellular arrhythmogenesis in paroxysmal AF patients. Previous studies suggested that increased calcium uptake resulting from phospholamban hyper-phosphorylation, and ryanodine receptor channel dysregulation by sarcoplasmatic reticulum increased spontaneous cellular activity in paroxysmal AF [43]. These findings provide important...
evidence for the role of calcium-dependent ectopic activity in paroxysmal AF, which are different from those of long-standing persistent AF patients that have profound alterations in L-type calcium currents and action potential durations [43]. These results provide opportunities to develop tailored therapeutic approaches for AF (Table 1 and Figure 1).

4. Fibroblast Growth Factor-23: A Key Link between Chronic Kidney Disease, Atrial Fibrillation and Heart Failure

Fibroblast growth factor-23 (FGF-23) is a bone-derived hormone that plays a central role in phosphate homeostasis. FGF-23 acts on the kidney to promote urinary phosphate excretion and to inhibit the production of 1,25-dihydroxyvitamin D, thereby reducing gastrointestinal absorption of dietary phosphate [44]. Circulating FGF-23 concentrations rise substantially with chronic kidney disease (CKD). In human studies, higher circulating concentrations of FGF-23 have been associated with increased left ventricular mass as well as incident heart failure, myocardial infarction, and cardiovascular death [45]. Increased cardiac hypertrophy induced by FGF-23 can lead to diastolic dysfunction and a rise in left ventricular filling pressures, resulting in left atrial dilation and fibrosis, an important structural substrate for AF initiation [46]. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) and Cardiovascular Health Study (CHS) showed an association between circulating FGF-23 concentration and incident AF [44]. In multivariable analysis models, each two-fold-higher FGF-23 concentration was associated with a more than 30% AF risk increase. Therefore, higher circulating FGF-23 concentration is associated with incident AF and may partially explain the link between CKD, HF and AF [44] (Figure 2).

Figure 2. Fibroblast growth factor-23 (FGF-23): A key link between chronic kidney disease, atrial fibrillation and heart failure. CKD: chronic kidney disease; LVH: Left ventricular hypertrophy; CV: cardiovascular; ↑ up-regulation; ↓ down-regulation.
5. Atrial Structure and Function Influence on Thromboembolic Risk and Heart Failure

Understanding the association between atrial structure and function with thromboembolic and HF risk is very important to improve preventive and therapeutic strategies. The Effective aNticoagulation with factor xA next GEneration in AF-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) study [47] evaluated left atrial (LA) size and function, according to the electrical burden of AF (paroxysmal, persistent, and permanent) as well as stroke risk expressed in the CHADS2 score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke). This study identified strong correlations between increasing abnormalities of LA structure and function with greater burdens of AF and higher CHADS2 score—an estimate of stroke risk. While the majority of AF subjects had LA enlargement, impairment of LA function was also demonstrated among a large number of subjects with normal LA size. These findings suggest that the assessment of LA function may add important information in the evaluation of the AF patient [48], in order to improve stroke risk stratification beyond that achieved with conventional clinical characteristics [49–51].

6. Obesity and Epicardial Fat Increase Atrial Arrhythmogenesis

Obesity increases the risk of developing HF, ischemic heart disease, and AF [52,53]. Chamber dilatation and hypertrophy are associated with obesity and may explain the increased risk of AF [54]. This epicardial adipose tissue is also associated with AF, presumably due to higher levels of inflammatory mediators, such as adipocytocines [55] and neurally-mediated mechanisms such as vagal modulation [56,57]. The direct contact of epicardial fat with the atria may induce direct atrial arrhythmogenic effects [55,58]. In the context of HF, epicardial fat prolongs LA action potentials duration, increasing calcium influx and LA contractility and triggered activity [59]. Since the epicardial fat is not evenly distributed over the atrial wall, it is possible that the action potentials prolongation effects of epicardial fat may contribute to larger atrial electrical dispersions and facilitate the maintenance of re-entrant circuits [60]. Abnormal epicardial fat has been associated with endothelial dysfunction [61], which in turn is associated with higher risk of stroke [62] and lower probability of conversion to sinus rhythm [63]. Epicardial fat in contact with the LA correlated with levels of soluble intercellular adhesion molecule 1 (sICAM-1) and von Willebrand factor (vWF), suggesting that epicardial adipose tissue may modulate endothelial function in patients with AF possibly through a paracrine mechanism [64].

In contrast to AF, patients with HF were found to have less epicardial fat mass and smaller adipocytes than controls [65], possibly due to systemic and local catabolic derangements and impaired tissue oxygenation in HF [65]. Consequently, the smaller cells size of HF adipocytes would produce lower concentrations of inflammatory cytokines and adipokines [66,67], providing a potential explanation for the better prognosis found in obese HF with reduced ejection fraction patients (HF-REF)—the so-called “obesity paradox”[52,68]. The “obesity paradox” is only observed in obese HF-REF patients. On the other hand, obesity, particularly central and/or visceral adiposity, is independently associated with diastolic dysfunction [69–72].
7. Abnormal Gene Expression in Atrial Fibrillation

The mechanisms underlying susceptibility to most forms of AF remain unknown [73]. Some forms of atrial fibrillation, especially “lone AF” may have a heritable pattern [74,75]. At the molecular level, the onset of HF is associated with reprogramming of gene expression, including down regulation of the α-myosin heavy chain (α-MHC) gene and sarcoplasmic reticulum calcium ATPase genes and reactivation of specific fetal cardiac genes such as atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP) [76]. Additionally, arrhythmias in general are frequent in patients with hereditary myopathies such as laminopathies, Emery-Dreifuss muscular dystrophy, myotonic dystrophy I, mitochondrial myopathies, fatty-acid oxidation defects, and dystrophinopathies which indicate that hereditary myopathies carry an increased risk for developing potentially severe arrhythmias and sudden death. Therefore, close follow-up and long-term rhythm surveillance may prevent fatal complications in these patients [77].

8. Heart Failure and Atrial Fibrillation: Treatment Implications

In general, the evidence on HF or AF treatments is generalizable to patients presenting with both diseases because it is unlikely that the proven benefit to one disease disappears when the other is simultaneously present. In addition, most of the trials testing specific treatments to AF or HF included a subset of patients who had both diseases, which further strengthens their external validity to this specific group of patients. Nevertheless, there are some specific therapeutic implications when managing patients with coexistent HF and AF that clinicians should be aware.

As previously discussed, AF is a robust and independent prognostic marker in HF populations. However, the conjectural benefit of rhythm control has never been empirically proved. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) [78] and the Atrial Fibrillation in Congestive Heart Failure (AF-CHF) [79] trials demonstrated similar all-cause HF incidence, hospitalization and overall mortality in both rhythm control and rate control groups. This discrepancy between the worse outcomes in AF patients compared to those in sinus rhythm is partially indicted to the limited efficacy, as well as to the significant adverse events of the available antiarrhythmic drugs. Other important determinant to this rhythm versus rate control decision is the presence of symptoms attributed to AF despite controlled heart rate. Despite some dissent results regarding quality of life (QoL) impact of these treatment strategies [80,81], the lower QoL in AF patients and its recognized detrimental hemodynamic impact legitimate the option for rhythm control in selected symptomatic AF patients. Conversely, it is appropriate to pursue rate rather than rhythm control if symptoms related to AF are deemed acceptable [82].

Several clinical trials have consistently shown the benefits of anticoagulation in AF, which is a powerful risk factor for stroke and thromboembolism. The decision to initiate anticoagulation therapy is adequately informed by thromboembolic risk stratification scores as CHADS2 (congestive HF, hypertension, age, diabetes, stroke) and CHA2DS2-Vasc (congestive HF, hypertension, age, diabetes, stroke, female gender, vascular disease) [82]. These scores assigns one point to each variable, other than age above 75 years or a previous history including a thromboembolic event, which gets two points. Hence, according to these scores HF and hypertension and coronary artery disease (CAD) carry the
same thromboembolic risk. However, HF seems to be associated with increased risk than diabetes or CAD [83], especially when LVEF is reduced [52]. Therefore, these scores may underestimate the thromboembolic risk in patients with AF and HF. In practical terms, when the score gives an intermediate risk (1 point), the AF patient who presents isolated HF should be considered at increased risk compared to others having 1-point due to diabetes, CAD or hypertension.

The efficacy of conventional HF drugs in primary prevention of AF remind us how interconnected these diseases are. Angiotensin-converting enzyme inhibitors [84], angiotensin receptor blockers [85], β-blockers [86] and mineralocorticoid receptor antagonists [87] had all been shown to reduce AF incidence in HF patients.

Cardiac resynchronization therapy (CRT) consists of a biventricular pacing in order to restore synchronicity of left and right ventricles activation. Several trials demonstrated a mortality benefit in HF populations, however the presence of AF has been significantly associated with a non-response to CRT [88]. This may be explained by a true smaller effect of CRT in AF patients, which usually are older, have more advanced HF and more comorbidities. An alternative explanation is the suboptimal delivery of biventricular pacing that AF patients are more likely to have because of the loss of biventricular capture due to pseudo-fusion or fusion beats. The underrepresentation of AF in CRT trials and underpowered studies to detect differences in HF populations with AF makes less clear the clinical benefits of CRT in this specific subgroup of patients [89]. Despite the weak evidence, the general opinion is that symptomatic AF patients (class III and IV of New York Heart Association) may benefit from CRT provided that biventricular pacing is close to 100%, using either drugs or atrioventricular junction ablation [90].

9. Conclusions

AF and HF are two growing epidemics that often coexist due to common risk factors and shared pathophysiological mechanisms. The translation into the clinical practice of the significant advances in the comprehension of the underlying AF pathophysiology has been poor, as there is a lack of specific targeted treatments. Despite the numerous clinical trials that had addressed different aspects of treatment of patients with isolated HF or AF, few have focused on the management of patients with the combination of both diseases. Nevertheless, when managing a patient with HF and AF, the clinician should be aware of the prognostic significance and some therapeutic implications of this increasingly common disease combination.

Author Contributions

João Pedro Ferreira wrote the first draft of the manuscript, organized the tables and figure; reviewed the manuscript and added new sections in the revised manuscript; Mário Santos reviewed the manuscript and added new sections in the revised manuscript, improving the overall quality of the paper.

Conflicts of Interest

The authors declare no conflict of interest.
1. McMurray, J.J.; Adamopoulos, S.; Anker, S.D.; Auricchio, A.; Bohm, M.; Dickstein, K.; Falk, V.; Filippatos, G.; Fonseca, C.; Gomez-Sanchez, M.A.; et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology: Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur. J. Heart Fail.* 2012, 14, 803–869.

2. Roubille, F.; Tardif, J.C. New therapeutic targets in cardiology: Heart failure and arrhythmia: HCN Channels. *Circulation* 2013, 127, 1986–1996.

3. Go, A.S.; Hylek, E.M.; Phillips, K.A.; Chang, Y.; Henault, L.E.; Selby, J.V.; Singer, D.E. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* 2001, 285, 2370–2375.

4. Chugh, S.S.; Roth, G.A.; Gillum, R.F.; Mensah, G.A. Global burden of atrial fibrillation in developed and developing nations. *Glob. Heart* 2014, 9, 113–119.

5. Wang, T.J.; Larson, M.G.; Levy, D.; Vasan, R.S.; Leip, E.P.; Wolf, P.A.; D’Agostino, R.B.; Murabito, J.M.; Kannel, W.B.; Benjamin, E.J. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The framingham heart study. *Circulation* 2003, 107, 2920–2925.

6. Carson, P.E.; Johnson, G.R.; Dunkman, W.B.; Fletcher, R.D.; Farrell, L.; Cohn, J.N. The influence of atrial fibrillation on prognosis in mild to moderate heart failure: The V-HeFT studies: The V-HeFT VA cooperative studies group. *Circulation* 1993, 87, VI102–VI110.

7. Savelieva, I.; John Camm, A. Atrial fibrillation and heart failure: Natural history and pharmacological treatment. *Europace* 2004, 5 (Suppl. 1), S5–S19.

8. Connolly, S.J.; Ezekowitz, M.D.; Yusuf, S.; Eikelboom, J.; Oldgren, J.; Parekh, A.; Pogue, J.; Reilly, P.A.; Themeles, E.; Varrone, J.; et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 2009, 361, 1139–1151.

9. Patel, M.R.; Mahaffey, K.W.; Garg, J.; Pan, G.; Singer, D.E.; Hacke, W.; Breithardt, G.; Halperin, J.L.; Hankey, G.J.; Piccini, J.P.; et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* 2011, 365, 883–891.

10. Stevenson, W.G.; Stevenson, L.W.; Middlekauff, H.R.; Fonarow, G.C.; Hamilton, M.A.; Woo, M.A.; Saxon, L.A.; Natterson, P.D.; Steimle, A.; Walden, J.A.; et al. Improving survival for patients with atrial fibrillation and advanced heart failure. *J. Am. Coll. Cardiol.* 1996, 28, 1458–1463.

11. Mamas, M.A.; Caldwell, J.C.; Chacko, S.; Garratt, C.J.; Fath-Ordoubadi, F.; Neyses, L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur. J. Heart Fail.* 2009, 11, 676–683.

12. Cha, Y.M.; Redfield, M.M.; Shen, W.K.; Gersh, B.J. Atrial fibrillation and ventricular dysfunction: A vicious electromechanical cycle. *Circulation* 2004, 109, 2839–2843.

13. Burstein, B.; Nattel, S. Atrial fibrosis: Mechanisms and clinical relevance in atrial fibrillation. *J. Am. Coll. Cardiol.* 2008, 51, 802–809.
14. Nattel, S.; Burstein, B.; Dobrev, D. Atrial remodeling and atrial fibrillation: Mechanisms and implications. Circ. Arrhythm. Electrophysiol. 2008, 1, 62–73.

15. Tsai, C.T.; Lai, L.P.; Kuo, K.T.; Hwang, J.J.; Hsieh, C.S.; Hsu, K.L.; Tseng, C.D.; Tseng, Y.Z.; Chiang, F.T.; Lin, J.L. Angiotensin II activates signal transducer and activators of transcription 3 via Rac1 in atrial myocytes and fibroblasts: Implication for the therapeutic effect of statin in atrial structural remodeling. Circulation 2008, 117, 344–355.

16. Rosenkranz, S. TNF-β1 and angiotensin networking in cardiac remodeling. Cardiovasc. Res. 2004, 63, 423–432.

17. Verheule, S.; Sato, T.; Everett, T.T.; Engle, S.K.; Otten, D.; Rubart-von der Lohe, M.; Nakajima, H.O.; Nakajima, H.; Field, L.J.; Olgin, J.E. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TNF-β1. Circ. Res. 2004, 94, 1458–1465.

18. Liao, C.H.; Akazawa, H.; Tamagawa, M.; Ito, K.; Yasuda, N.; Kudo, Y.; Yamamoto, R.; Ozasa, Y.; Fujimoto, M.; Wang, P.; et al. Cardiac mast cells cause atrial fibrillation through PDGF-A-mediated fibrosis in pressure-overloaded mouse hearts. J. Clin. Invest. 2010, 120, 242–253.

19. Qu, Y.C.; Du, Y.M.; Wu, S.L.; Chen, Q.X.; Wu, H.L.; Zhou, S.F. Activated nuclear factor-κB and increased tumor necrosis factor-α in atrial tissue of atrial fibrillation. Scand. Cardiovasc. J. 2009, 43, 292–297.

20. Adam, O.; Lavall, D.; Theobald, K.; Hohl, M.; Grube, M.; Ameling, S.; Sussman, M.A.; Rosenkranz, S.; Kroemer, H.K.; Schafer, H.J.; et al. Rac1-induced connective tissue growth factor regulates connexin 43 and N-cadherin expression in atrial fibrillation. J. Am. Coll. Cardiol. 2010, 55, 469–480.

21. Sulciner, D.J.; Irani, K.; Yu, Z.X.; Ferrans, V.J.; Goldschmidt-Clermont, P.; Finkel, T. Rac1 regulates a cytokine-stimulated, redox-dependent pathway necessary for NF-κB activation. Mol. Cell. Biol. 1996, 16, 7115–7121.

22. Gao, G.; Dudley, S.C., Jr. Redox regulation, NF-κb, and atrial fibrillation. Antioxid. Redox Signal. 2009, 11, 2265–2277.

23. Adam, O.; Frost, G.; Custodis, F.; Sussman, M.A.; Schafer, H.J.; Bohm, M.; Laufs, U. Role of Rac1 GTPase activation in atrial fibrillation. J. Am. Coll. Cardiol. 2007, 50, 359–367.

24. Goette, A.; Lendeckeckel, U.; Klein, H.U. Signal transduction systems and atrial fibrillation. Cardiovasc. Res. 2002, 54, 247–258.

25. Brilla, C.G.; Scheer, C.; Rupp, H. Angiotensin II and intracellular calcium of adult cardiac fibroblasts. J. Mol. Cell Cardiol. 1998, 30, 1237–1246.

26. Patel, B.M.; Mehta, A.A. Aldosterone and angiotensin: Role in diabetes and cardiovascular diseases. Eur. J. Pharmacol. 2012, 697, 1–12.

27. Harrison, D.G.; Cai, H.; Landmesser, U.; Griendling, K.K. Interactions of angiotensin II with NAD(P)H oxidase, oxidant stress and cardiovascular disease. J. Renin Angiotensin Aldosterone Syst. 2003, 4, 51–61.

28. Teekakirikul, P.; Eminaga, S.; Toka, O.; Alcalai, R.; Wang, L.; Wakimoto, H.; Nayor, M.; Konno, T.; Gorham, J.M.; Wolf, C.M.; et al. Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires TNF-β. J. Clin. Invest. 2010, 120, 3520–3529.
29. Takeda, N.; Manabe, I.; Uchino, Y.; Eguchi, K.; Matsumoto, S.; Nishimura, S.; Shindo, T.; Sano, M.; Otsu, K.; Snider, P.; et al. Cardiac fibroblasts are essential for the adaptive response of the murine heart to pressure overload. *J. Clin. Investig.* **2010**, *120*, 254–265.

30. Aleong, R.G.; Sauer, W.H.; Murphy, G.A.; Port, J.D.; Anand, I.S.; Fiuzat, M.; O’Connor, C.M.; Abraham, W.T.; Liggett, S.B.; Bristow, M.R. Prevention of atrial fibrillation by bucindolol is dependent on the β1389 Arg/Gly adrenergic receptor polymorphism. *JACC Heart Fail.* **2013**, *1*, 338–344.

31. Kao, D.P.; Davis, G.; Aleong, R.; O’Connor, C.M.; Fiuzat, M.; Carson, P.E.; Anand, I.S.; Plehn, J.F.; Gottlieb, S.S.; Silver, M.A.; et al. Effect of bucindolol on heart failure outcomes and heart rate response in patients with reduced ejection fraction heart failure and atrial fibrillation. *Eur. J. Heart Fail.* **2013**, *15*, 324–333.

32. Oral, H.; Crawford, T.; Frederick, M.; Gadeela, N.; Wimmer, A.; Dey, S.; Sarrazin, J.F.; Kuhne, M.; Chalfoun, N.; Wells, D.; et al. Inducibility of paroxysmal atrial fibrillation by isoproterenol and its relation to the mode of onset of atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **2008**, *19*, 466–470.

33. Sharifov, O.F.; Fedorov, V.V.; Beloshapko, G.G.; Glukhov, A.V.; Yushmanova, A.V.; Rosenshtraukh, L.V. Roles of adrenergic and cholinergergic stimulation in spontaneous atrial fibrillation in dogs. *J. Am. Coll. Cardiol.* **2004**, *43*, 483–490.

34. Wang, C.; Zhang, Y.J.; Wang, Y.L.; Xu, Y.F.; Liu, S.; Chen, Z.Y.; Liu, L.L. Effect of dipfluzine on delayed afterdepolarizations and triggered activity induced by isoprenaline in human atrial fibers. *Yao Xue Xue Bao (in Chinese)* **2006**, *41*, 184–187.

35. Van der Velden, H.M.; Ausma, J.; Rook, M.B.; Hellemons, A.J.; van Veen, T.A.; Allessie, M.A.; Jongsma, H.J. Gap junctional remodeling in relation to stabilization of atrial fibrillation in the goat. *Cardiovasc. Res.* **2000**, *46*, 476–486.

36. Satoh, T.; Zipes, D.P. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **1996**, *7*, 833–842.

37. Allessie, M.A.; Boyden, P.A.; Camm, A.J.; Kleber, A.G.; Lab, M.J.; Legato, M.J.; Rosen, M.R.; Schwartz, P.J.; Spooner, P.M.; van Wagoner, D.R.; et al. Pathophysiology and prevention of atrial fibrillation. *Circulation* **2001**, *103*, 769–777.

38. Daoud, E.G.; Bogun, F.; Goyal, R.; Harvey, M.; Man, K.C.; Strickberger, S.A.; Morady, F. Effect of atrial fibrillation on atrial refractoriness in humans. *Circulation* **1996**, *94*, 1600–1606.

39. Hasenfuss, G.; Reinecke, H.; Studer, R.; Meyer, M.; Pieske, B.; Holtz, J.; Holubarsch, C.; Posival, H.; Just, H.; Drexler, H. Relation between myocardial function and expression of sarcoplasmic reticulum Ca^{2+}-ATPase in failing and nonfailing human myocardium. *Circ. Res.* **1994**, *75*, 434–442.

40. Voigt, N.; Li, N.; Wang, Q.; Wang, W.; Trafford, A.W.; Abu-Taha, I.; Sun, Q.; Wieland, T.; Ravens, U.; Nattel, S.; et al. Enhanced sarcoplasmic reticulum Ca^{2+} leak and increased Na^{+}–Ca^{2+} exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. *Circulation* **2012**, *125*, 2059–2070.

41. Hove-Madsen, L.; Llach, A.; Bayes-Genis, A.; Roura, S.; Rodriguez Font, E.; Aris, A.; Cinca, J. Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes. *Circulation* **2004**, *110*, 1358–1363.
42. Neef, S.; Dybkova, N.; Sossalla, S.; Ort, K.R.; Fluschnik, N.; Neumann, K.; Seipel, R.; Schondube, F.A.; Hasenfuss, G.; Maier, L.S. CaMKII-dependent diastolic SR Ca$^{2+}$ leak and elevated diastolic Ca$^{2+}$ levels in right atrial myocardium of patients with atrial fibrillation. **Circ. Res.** 2010, **106**, 1134–1144.

43. Voigt, N.; Heijman, J.; Wang, Q.; Chiang, D.Y.; Li, N.; Karck, M.; Wehrens, X.H.; Nattel, S.; Dobrev, D. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. **Circulation** 2014, **129**, 145–156.

44. Mathew, J.S.; Sachs, M.C.; Katz, R.; Patton, K.K.; Heckbert, S.R.; Hoofnagle, A.N.; Alonso, A.; Chonchol, M.; Deo, R.; Ix, J.H.; et al. Fibroblast growth factor-23 and left ventricular hypertrophy in chronic kidney disease. **Circulation** 2009, **119**, 2545–2552.

45. Gutierrez, O.M.; Januzzi, J.L.; Isakova, T.; Laliberte, K.; Smith, K.; Collerone, G.; Sarwar, A.; Hoffmann, U.; Coglianese, E.; Christenson, R.; et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. **Circulation** 2009, **119**, 2545–2552.

46. Rosenberg, M.A.; Manning, W.J. Diastolic dysfunction and risk of atrial fibrillation: A mechanistic appraisal. **Circulation** 2012, **126**, 2353–2362.

47. Gupta, D.K.; Shah, A.M.; Giugliano, R.P.; Ruff, C.T.; Antman, E.M.; Grip, L.T.; Deenadayalu, N.; Hoffman, E.; Patel, I.; Shi, M.; et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. **Eur. Heart J.** 2014, **35**, 1457–1465.

48. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. **Stroke** 2008, **39**, 1901–1910.

49. Dittrich, H.C.; Pearce, L.A.; Aisinger, R.W.; McBride, R.; Webel, R.; Zabalgoitia, M.; Pennock, G.D.; Safford, R.E.; Rothbart, R.M.; Halperin, J.L.; et al. Left atrial diameter in nonvalvular atrial fibrillation: An echocardiographic study: Stroke prevention in atrial fibrillation investigators. **Am. Heart J.** 1999, **137**, 494–499.

50. Gage, B.F.; Waterman, A.D.; Shannon, W.; Boechler, M.; Rich, M.W.; Radford, M.J. Validation of clinical classification schemes for predicting stroke: Results from the national registry of atrial fibrillation. **JAMA** 2001, **285**, 2864–2870.

51. Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: A prospective study of 1066 patients from 3 clinical trials. **Arch. Intern. Med.** 1998, **158**, 1316–1320.

52. Kenchaiah, S.; Evans, J.C.; Levy, D.; Wilson, P.W.; Benjamin, E.J.; Larson, M.G.; Kannel, W.B.; Vasan, R.S. Obesity and the risk of heart failure. **N. Engl. J. Med.** 2002, **347**, 305–313.

53. Morricone, L.; Malavazos, A.E.; Coman, C.; Donati, C.; Hassan, T.; Caviezel, F. Echocardiographic abnormalities in normotensive obese patients: Relationship with visceral fat. **Obes. Res.** 2002, **10**, 489–498.

54. Psaty, B.M.; Manolio, T.A.; Kuller, L.H.; Kronmal, R.A.; Cushman, M.; Fried, L.P.; White, R.; Furberg, C.D.; Rautaharju, P.M. Incidence of and risk factors for atrial fibrillation in older adults. **Circulation** 1997, **96**, 2455–2461.

55. Lin, Y.K.; Chen, Y.J.; Chen, S.A. Potential atrial arrhythmogenicity of adipocytes: Implications for the genesis of atrial fibrillation. **Med. Hypotheses** 2010, **74**, 1026–1029.
56. Nagashima, K.; Okumura, Y.; Watanabe, I.; Nakai, T.; Ohkubo, K.; Kofune, M.; Mano, H.; Sonoda, K.; Hiro, T.; Nikaido, M.; et al. Does location of epicardial adipose tissue correspond to endocardial high dominant frequency or complex fractionated atrial electrogram sites during atrial fibrillation? *Circ. Arrhythm. Electrophysiol.* 2012, 5, 676–683.

57. Chen, P.S.; Turker, I. Epicardial adipose tissue and neural mechanisms of atrial fibrillation. *Circ. Arrhythm. Electrophysiol.* 2012, 5, 618–620.

58. Batal, O.; Schoenhagen, P.; Shao, M.; Ayyad, A.E.; van Wagoner, D.R.; Halliburton, S.S.; Tchou, P.J.; Chung, M.K. Left atrial epicardial adiposity and atrial fibrillation. *Circ. Arrhythm. Electrophysiol.* 2010, 3, 230–236.

59. Lin, Y.K.; Chen, Y.C.; Chang, S.L.; Lin, Y.J.; Chen, J.H.; Yeh, Y.H.; Chen, S.A.; Chen, Y.J. Heart failure epicardial fat increases atrial arrhythmogenesis. *Int. J. Cardiol.* 2013, 167, 1979–1983.

60. Chen, Y.J.; Tai, C.T.; Chiou, C.W.; Wen, Z.C.; Chan, P.; Lee, S.H.; Chen, S.A. Inducibility of atrial fibrillation during atrioventricular pacing with varying intervals: Role of atrial electrophysiology and the autonomic nervous system. *J. Cardiovasc. Electrophysiol.* 1999, 10, 1578–1585.

61. Aydin, H.; Toprak, A.; Deynelli, O.; Yazici, D.; Tarcin, O.; Sancak, S.; Yavuz, D.; Akalin, S. Epicardial fat tissue thickness correlates with endothelial dysfunction and other cardiovascular risk factors in patients with metabolic syndrome. *Metab. Syndr. Relat. Disord.* 2010, 8, 229–234.

62. Pinto, A.; Tuttolomondo, A.; Casuccio, A.; di Raimondo, D.; di Sciacca, R.; Arnao, V.; Licata, G. Immuno-inflammatory predictors of stroke at follow-up in patients with chronic non-valvular atrial fibrillation (NVAF). *Clin. Sci. (Lond.)* 2009, 116, 781–789.

63. Acevedo, M.; Corbalan, R.; Braun, S.; Pereira, J.; Gonzalez, I.; Navarrete, C. Biochemical predictors of cardiac rhythm at 1 year follow-up in patients with non-valvular atrial fibrillation. *J. Thromb. Thrombolysis* 2012, 33, 383–388.

64. Girerd, N.; Scridon, A.; Bessiere, F.; Chauveau, S.; Geloen, A.; Boussel, L.; Morel, E.; Chevalier, P. Periatrial epicardial fat is associated with markers of endothelial dysfunction in patients with atrial fibrillation. *PLoS One* 2013, 8, e77167.

65. Khan, R.S.; Kato, T.S.; Chokshi, A.; Chew, M.; Yu, S.; Wu, C.; Singh, P.; Cheema, F.H.; Takayama, H.; Harris, C.; et al. Adipose tissue inflammation and adiponectin resistance in patients with advanced heart failure: Correction after ventricular assist device implantation. *Circ. Heart Fail.* 2012, 5, 340–348.

66. Vazquez-Vela, M.E.; Torres, N.; Tovar, A.R. White adipose tissue as endocrine organ and its role in obesity. *Arch. Med. Res.* 2008, 39, 715–728.

67. Fei, J.; Cook, C.; Blough, E.; Santanam, N. Age and sex mediated changes in epicardial fat adipokines. *Atherosclerosis* 2010, 212, 488–494.

68. Lavie, C.J.; Milani, R.V.; Ventura, H.O. Obesity and cardiovascular disease: Risk factor, paradox, and impact of weight loss. *J. Am. Coll. Cardiol.* 2009, 53, 1925–1932.

69. Fontes-Carvalho, R.; Fontes-Oliveira, M.; Sampaio, F.; Mancio, J.; Bettencourt, N.; Teixeira, M.; Rocha Goncalves, F.; Gama, V.; Leite-Moreira, A. Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction. *Am. J. Cardiol.* 2014, 114, 1663–1669.
70. Canepa, M.; Strait, J.B.; Abramov, D.; Milaneschi, Y.; AlGhatrif, M.; Moni, M.; Ramachandran, R.; Najjar, S.S.; Brunelli, C.; Abraham, T.P.; et al. Contribution of central adiposity to left ventricular diastolic function (from the baltimore longitudinal study of aging). *Am. J. Cardiol.* **2012**, *109*, 1171–1178.

71. Russo, C.; Jin, Z.; Homma, S.; Rundek, T.; Elkind, M.S.; Sacco, R.L.; di Tullio, M.R. Effect of obesity and overweight on left ventricular diastolic function: A community-based study in an elderly cohort. *J. Am. Coll. Cardiol.* **2011**, *57*, 1368–1374.

72. Konishi, M.; Sugiyama, S.; Sugamura, K.; Nozaki, T.; Matsubara, J.; Akiyama, E.; Utsunomiya, D.; Matsuzawa, Y.; Yamashita, Y.; Kimura, K.; et al. Accumulation of pericardial fat correlates with left ventricular diastolic dysfunction in patients with normal ejection fraction. *J. Cardiol.* **2012**, *59*, 344–351.

73. Chugh, S.S.; Blackshear, J.L.; Shen, W.K.; Hammill, S.C.; Gersh, B.J. Epidemiology and natural history of atrial fibrillation: Clinical implications. *J. Am. Coll. Cardiol.* **2001**, *37*, 371–378.

74. Arnar, D.O.; Thorvaldsson, S.; Manolio, T.A.; Thorgeirsson, G.; Kristjansson, K.; Hakonarson, H.; Stefansson, K. Familial aggregation of atrial fibrillation in iceland. *Eur. Heart J.* **2006**, *27*, 708–712.

75. Ellinor, P.T.; Lunetta, K.L.; Albert, C.M.; Glazer, N.L.; Smith, A.V.; Arking, D.E.; Muller-Nurasyid, M.; Krijthe, B.P.; Lubitz, S.A.; et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat. Genet.* **2012**, *44*, 670–675.

76. Duygu, B.; Poels, E.M.; da Costa Martins, P.A. Genetics and epigenetics of arrhythmia and heart failure. *Front. Genet.* **2013**, *4*, 219.

77. Finsterer, J.; Stollberger, C.; Keller, H. Arrhythmia-related workup in hereditary myopathies. *J. Electrocardiol.* **2012**, *45*, 376–384.

78. Corley, S.D.; Epstein, A.E.; DiMarco, J.P.; Domanski, M.J.; Geller, N.; Greene, H.L.; Josephson, R.A.; Kellen, J.C.; Klein, R.C.; Krahn, A.D.; et al. Relationships between sinus rhythm, treatment, and survival in the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. *Circulation* **2004**, *109*, 1509–1513.

79. Roy, D.; Talajic, M.; Nattel, S.; Wyse, D.G.; Dorian, P.; Lee, K.L.; Bourassa, M.G.; Arnold, J.M.; Buxton, A.E.; Camm, A.J.; et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N. Engl. J. Med.* **2008**, *358*, 2667–2677.

80. Shelton, R.J.; Clark, A.L.; Goode, K.; Rigby, A.S.; Houghton, T.; Kaye, G.C.; Cleland, J.G. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II study). *Heart* **2009**, *95*, 924–930.

81. Hagens, V.E.; Ranchor, A.V.; van Sonderen, E.; Bosker, H.A.; Kamp, O.; Tijssen, J.G.; Kingma, J.H.; Crijns, H.J.; van Gelder, I.C. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation: Results from the rate control versus electrical cardioversion (RACE) study. *J. Am. Coll. Cardiol.* **2004**, *43*, 241–247.

82. Camm, A.J.; Kirchhof, P.; Lip, G.Y.; Schotten, U.; Savelieva, I.; Ernst, S.; van Gelder, I.C.; Al-Attar, N.; Hindricks, G.; Prendergast, B.; et al. 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**, *31*, 2369–2429.

83. Wolf, P.A.; Abbott, R.D.; Kannel, W.B. Atrial fibrillation as an independent risk factor for stroke: The framingham study. *Stroke* **1991**, *22*, 983–988.
84. Pedersen, O.D.; Bagger, H.; Kober, L.; Torp-Pedersen, C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation* **1999**, *100*, 376–380.

85. Ducharme, A.; Swedberg, K.; Pfeffer, M.A.; Cohen-Solal, A.; Granger, C.B.; Maggioni, A.P.; Michelson, E.L.; McMurray, J.J.; Olsson, L.; Rouleau, J.L.; *et al.* Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) program. *Am. Heart J.* **2006**, *151*, 985–991.

86. Nasr, I.A.; Bouzamondo, A.; Hulot, J.S.; Dubourg, O.; le Heuzey, J.Y.; Lechat, P. Prevention of atrial fibrillation onset by β-blocker treatment in heart failure: A meta-analysis. *Eur. Heart J.* **2007**, *28*, 457–462.

87. Swedberg, K.; Zannad, F.; McMurray, J.J.; Krum, H.; van Veldhuisen, D.J.; Shi, H.; Vincent, J.; Pitt, B. Eplerenone and atrial fibrillation in mild systolic heart failure: Results from the EMPHASIS-HF (eplerenone in mild patients hospitalization and survival study in heart failure) study. *J. Am. Coll. Cardiol.* **2012**, *59*, 1598–1603.

88. Wilton, S.B.; Leung, A.A.; Ghali, W.A.; Faris, P.; Exner, D.V. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: A systematic review and meta-analysis. *Heart Rhythm.* **2011**, *8*, 1088–1094.

89. Lopes, C.; Pereira, T.; Barra, S. Cardiac resynchronization therapy in patients with atrial fibrillation: A meta-analysis. *Rev. Port. Cardiol.* **2014**, *33*, 717–725.

90. Brignole, M.; Auricchio, A.; Baron-Esquivias, G.; Bordachar, P.; Boriani, G.; Breithardt, O.A.; Cleland, J.; Deharo, J.C.; Delgado, V.; Elliott, P.M.; *et al.* 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: The task force on cardiac pacing and resynchronization therapy of the European society of cardiology (ESC): Developed in collaboration with the European heart rhythm association (EHRA). *Eur. Heart J.* **2013**, *15*, 1070–1118.

© 2015 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/).