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Atrial Fibrosis and the Mechanisms of Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is commonly associated with congestive heart failure (CHF), and CHF has been shown to be associated with atrial structural remodeling resulting in fibrosis. This atrial interstitial fibrosis has been seen in patients with CHF and animal models of pacing induced heart failure. With atrial fibrosis, conduction abnormalities result in an increase in AF vulnerability. The mechanism of AF that is associated with CHF is still under debate as both focal and reentrant mechanisms have been observed in animal models of CHF. However, recent studies utilizing frequency domain analysis have shown that the AF within this model is characterized by discrete stable, high-frequency areas. The precise signalling processes involved in the development of atrial fibrosis are unknown. Angiotensin appears to play some role, since inhibition of ACE (or ARB) blunt atrial fibrosis in animal models of heart failure and decrease the incidence of AF in patients with heart failure. TGFβ1 also seems to play an important role. Mouse models that overexpress TGFβ1 have profound atrial fibrosis and atrial fibrillation (with normal ventricles). Heart failure in canine models also produces increases in atrial TGFβ1 expression and inhibition of this prevents atrial fibrosis and the development of a substrate for atrial fibrillation. Atrial fibrosis appears to play a role in the development of a vulnerable substrate for AF, especially in the setting of CHF.

Introduction

Atrial fibrillation (AF) is a common clinical arrhythmia, present in 5% of people older than 65. It is commonly associated with congestive heart failure (CHF) with the heart failure creating a substrate for AF and complicating therapy for these patients.[1] Theoretical models have implicated atrial interstitial fibrosis as a substrate for AF.[2, 3] Atrial interstitial fibrosis has been shown to increase with age in humans and has been observed in patients with AF[4, 5], in animal models of aging[6, 7], and in CHF[8]. This atrial interstitial fibrosis has been shown to increase AF vulnerability in animal models of CHF[8–10] and in a transgenic mouse model for selective atrial fibrosis[11]. Through these studies, it has been shown that atrial fibrosis creates a substrate that promotes AF. The mechanism of AF is still under debate as mechanisms of multiple wavelets[12, 13], focal sources[14], and mother rotor[15, 16] have been proposed and seen in a variety of animal models. However, very few studies have been performed investigating the mechanisms of AF in the presence of heart failure. Because of this, the mechanism of AF in this model is still not understood.

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Evidence for Atrial Fibrosis in Patients

Correlative data in biopsy and autopsy specimens from patients with AF have uncovered the presence of atrial fibrosis[5, 17–20]. Increased amounts of fibrosis have been seen in the atria of patients with AF as opposed to those in sinus rhythm[5, 17, 18], and this fibrosis has been correlated to decreasing amounts of connexin 43 expression.[5, 18] Atrial fibrosis has also been seen in patients who develop post-operative AF as compared to those patients who remain in sinus rhythm.[19, 20] While all of these data convincingly demonstrate that patients with AF have increased levels of atrial fibrosis compared to patients in sinus rhythm, these studies are correlative and do not investigate the mechanism behind the fibrosis accumulation or its effects on the electrophysiological properties of the atria.

In order to gain some insight into the effects of fibrosis on the electrophysiological properties of the atria, Sanders et al studied the electrical remodeling of the atria in patients with symptomatic congestive heart failure compared to controls[21]. Importantly, this study investigated patients with CHF but had no history of AF. This study showed that patients with CHF had increased atrial effective refractory periods, prolonged conduction times, and decreased bipolar voltage signal amplitudes than patients without CHF.

Canine Models of CHF and AF

A study by Li et al was the first to show that CHF in dogs (created by ventricular tachy pacing (VTP)) produced atrial interstitial fibrosis, which in turn produced disrupted conduction throughout the atria and an increased vulnerability to AF.[8] Studies have also examined the electrical properties of the atria in this model in terms of both ionic remodeling and gap junction distribution.[9, 22–24] These studies showed that the electrical properties of the atria did not contribute to the increased AF vulnerability in this model, and that atrial fibrosis played the key role in the AF substrate by causing an increase in conduction heterogeneity.

AF mechanisms with fibrosis

Multiple wavelets, focal sources and reentrant mechanisms of ‘mother rotor’ and spiral waves have been proposed as mechanisms for AF[12–16]. Which mechanism of AF is characteristic in a setting of atrial fibrosis is unknown, as evidence exists for both reentry and discrete, stable foci as an AF mechanism in dogs with pacing induced CHF. Li et al showed a mechanism of macroreentry with conduction abnormalities providing the mileu for AF propagation before termination with dofetilide, an I_{Kr} channel blocker. [25] In contrast, this study also showed that in a model of rapid atrial pacing (RAP), multiple wavelets was demonstrated to be the likely mechanism, and dofetilide was ineffective in terminating the AF. The RAP model has atrial electrical remodeling and little in the way of structural remodeling. The CHF model does not have any significant atrial electrical remodeling (at least none that contributes substantially to the AF substrate—see discussion above) but has substantial atrial structural remodeling.[8, 26] In a separate study comparing endocardial versus epicardial activation, this same group again showed an AF mechanism of macroreentry in dogs with CHF.[27] Stambler et al suggested that AF in the setting of CHF in dogs was focal in origin caused by triggered activity.[28] This triggered activity was shown to be produced by delayed afterdepolarizations (DAD) initiated by intracellular Ca^{+2} overload. Drugs that reduced intracellular Ca^{+2} levels (verapamil, flunarazine, ryanodine) all terminated AF. Fenelon et al expanded on this study by performing biatrial mapping in dogs with CHF and showed that the majority of AF episodes had a focal mechanism.[29] Focal radiofrequency catheter ablation was then attempted and was successful in 67% of the animals studied. Ryu et al performed FFT analysis on the recorded AF electrograms in dogs with CHF. The authors demonstrated that the AF had stable drivers in both the LA and RA, and confirmed this with activation mapping.[30] In 7 of 12 dogs studied, two distinct foci were seen - one in the RA and one in the LA with different frequencies and

fibrillatory conduction emanating out from the driver region. Discrete, stable, high frequency areas were also seen as the characteristics of the AF in a CHF dog model in a study by Everett et al.[31] Using frequency domain analysis, stable, high frequency areas were seen as the characteristic of AF in dogs with pacing induced heart failure. While Ryu et al showed multiple drivers during the same episode of AF, these high frequency areas were seen in either the RA or the LA and there was a steep frequency gradient away from these sites. Upon further inspection of unipolar electrograms at this site, fractionated electrograms were seen with low organization levels. In this study, it was also shown that these high frequency areas could occur in either the RA or LA. In contrast, no discrete, high frequency areas were seen in a model of RAP. It has also been suggested that the focal sources could be originating from the pulmonary veins in this CHF dog model of AF.[32] Chen et al performed high density mapping of the pulmonary veins during AF in dogs with CHF. In half of the AF episodes recorded in the CHF model, focal activation was seen from within the vein independent of the left atrium. This type of activation was not seen in any of the AF in controls as the pulmonary veins were activated passively from wavefronts originating from the left atrium.

Mechanism of Atrial Fibrosis

The precise mechanisms and signaling pathways involved in the development of atrial fibrosis is currently unknown. It does appear, however, that the atrium is more susceptible to atrial fibrosis than the ventricle and currently, 3 interrelated pathways appear to be involved—the rennin-angiotensin system, TGFβ1 and the oxidative stress pathways.

Studies have shown that the rennin-angiotensin system plays a role in cardiac structural remodeling and in the development of myocardial fibrosis in several diseases states including CHF[33], myocardial infarction[34], and cardiomyopathy[35]. Transgenic mouse models of ACE overexpression have shown to result in atrial fibrosis[36]. Several clinical and animal studies have shown that the use of ACE inhibitors with CHF reduces the occurrence of AF and AF vulnerability[37–40]. With the use of enalapril in canines with either CHF or rapid atrial pacing, it was shown that there was a significant attenuation of atrial fibrosis and a decrease in AF duration[37, 41]. In another study, decreased levels of atrial fibrosis and decreased AF inducibility and duration were seen with Cilazapril[42]. Similar results were seen when an angiotensin II type 1 receptor blocker Candesartan was administered to dogs[43]. This study also showed a decrease in AF duration along with a decrease in the levels of atrial fibrosis. This same drug has been shown to prevent atrial structural remodeling and fibrosis in rats[44].

Similar to the animal studies, Goette et al[45] reported elevated Ang II concentration with increased ERK activation in patients with atrial fibrosis and AF. One study has shown that ACE inhibitors reduced fibrosis in patients with lone AF [46]. Several retrospective clinical studies support the role of the rennin-angiotensin system as well by demonstrating a decrease in the incidence of AF in patients treated with ACE inhibitors or angiotensin-receptor blockers (ARBs), mostly in the setting of depressed LV function[46–53]. Use of ACE inhibitors has also been shown to prevent the progression of paroxysmal AF to chronic AF[47], and in increasing the efficacy of electrical cardioversion of AF[51, 52]. These clinical data suggest that the use of an ACE inhibitor may be useful to delay progression of atrial fibrosis and AF.

Role of TGF β1

TGFβ1 has been implicated in tissue wound healing and in the development of fibrosis. TGF-β1 expression has been shown to increase myocardial fibrosis[54]. In a transgenic mouse model that overexpresses a constitutively active transforming growth factor TGF-β1[11], there was selective atrial interstitial fibrosis, while ventricular histology was normal. This occurred despite equal overexpression of TGFβ1 in the atrium and the ventricles, This increase in atrial fibrosis was shown to correspond to an increase in conduction heterogeneity and AF

vulnerability.[11] Cellular electrophysiology was not affected by the TGFβ1. This study demonstrated that atrial fibrosis alone is a sufficient substrate for AF and that TGFβ1 may play an important role in the genesis of atrial fibrosis. Interestingly, this mouse model also suggests that the atrium is more susceptible to the development of atrial fibrosis, at least in response to high TGFβ1 levels.

In another study by the same group, the drug pirfenidone (PFD) was used to target the expression of TGF-β1[26]. PFD has been shown to significantly reduce expression of TGF-β1 with a concomitant reduction in tissue fibrosis in multiple experimental animal models, including those of lung,[55] hepatic,[56] and renal[57–59] fibrosis. Similar results were observed in the experimental model of CHF as it resulted in an increase in TGF-β1 expression and atrial fibrosis, and PFD treatment resulted in a significant reduction in TGF-β1 expression and atrial fibrosis. This reduction in atrial fibrosis also corresponded to a decrease in conduction abnormalities and in AF vulnerability[26]. TGF- β1 may be an interesting therapeutic target as more is learned about the precise pathways involved in the development of atrial fibrosis.

Along with atrial fibrosis, inflammation and oxidative stress may play an important role in promoting AF[60] as increased levels of C-reactive protein (CRP)[61, 62] and evidence of oxidative injury are seen during AF[63]. In a transgenic mouse model of cardiomyopathy that overexpressed TNF-α, Saba et al found both increased atrial fibrosis and abnormalities in action potential propagation and calcium handling in atrial myocytes with an increased susceptibility to atrial arrhythmias[60]. In the clinical arena, Chung et al showed that CRP, a marker of systemic inflammation, was elevated in patients with AF[61]. This study was then taken a step further and Aviles et al showed that elevated CRP levels can also predict those patients who are at an increased risk of developing AF[62].

Conclusion

Animal models of CHF are associated with an increase in atrial interstitial fibrosis. This increase in fibrosis has been shown to cause abnormal conduction through the atria creating a substrate for AF. The mechanism(s) of AF produced by the substrate of atrial fibrosis and CHF is still controversial as both macroreentry and focal sources that could be originating from RA, LA or the pulmonary veins have been demonstrated. Due to these multiple AF mechanisms seen in the presence of atrial fibrosis, more studies need to be performed to define which mechanism or mechanisms are associated with AF within this setting. Additionally, the molecular pathways involved in atrial fibrosis are beginning to emerge. While the rennin-angiotensin system and TGFβ1 may play an important role, identifying downstream molecules important in the genesis of fibrosis specifically in the atrium will be important in developing new therapeutic strategies aimed at preventing or reversing structural remodeling in the atrium. Finally, atrial fibrosis may be compensatory, but there are no data to suggest whether it is beneficial.

References

1. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquie JL, Scavee C, Bordachar P, Clementy J, Haissaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med Dec 2;2004 351(23):2373–2383. [PubMed: 15575053]
2. Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias . Pacing Clin Electrophysiol Feb;1997 20(2 Pt 2):397–413. [PubMed: 9058844]
3. Spach MS, Josephson ME. Initiating reentry: the role of nonuniform anisotropy in small circuits. J Cardiovasc Electrophysiol Feb;1994 5(2):182–209. [PubMed: 8186887]

4. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation Aug 19;1997 96(4):1180–1184. [PubMed: 9286947]
5. Kostin S, Klein G, Szalay Z, Hein S, Bauer EP, Schaper J. Structural correlate of atrial fibrillation in human patients. Cardiovasc Res May;2002 54(2):361–379. [PubMed: 12062341]
6. Anyukhovsky EP, Sosunov EA, Plotnikov A, Gainullin RZ, Jhang JS, Marboe CC, Rosen MR. Cellular electrophysiologic properties of old canine atria provide a substrate for arrhythmogenesis. Cardiovasc Res May;2002 54(2):462–469. [PubMed: 12062351]
7. Hayashi H, Wang C, Miyauchi Y, Omichi C, Pak HN, Zhou S, Ohara T, Mandel WJ, Lin SF, Fishbein MC, Chen PS, Karagueuzian HS. Aging-related increase to inducible atrial fibrillation in the rat model. J Cardiovasc Electrophysiol Aug;2002 13(8):801–808. [PubMed: 12212701]
8. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation Jul 6;1999 100(1):87–95. [PubMed: 10393686]
9. Guerra JM, Everett THt, Lee KW, Wilson E, Olgin JE. Effects of the gap junction modifier rotigaptide (ZP123) on atrial conduction and vulnerability to atrial fibrillation. Circulation Jul 11;2006 114(2): 110–118. [PubMed: 16818812]
10. Lee KW, Everett THt, Rahmutula D, Guerra JM, Wilson E, Ding C, Olgin JE. Pirfenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. Circulation Oct 17;2006 114(16):1703–1712. [PubMed: 17030685]
11. Verheule S, Sato T, Everett Tt, Engle SK, Otten D, Rubart-von der Lohe M, Nakajima HO, Nakajima H, Field LJ, Olgin JE. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. Circ Res Jun 11;2004 94(11):1458–1465. [PubMed: 15117823]
12. Allessie, M.; Lammers, WJEP.; Bonke, FIM.; Hollen, J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes, DP.; Jalife, J., editors. Cardiac Electrophysiology and Arrhythmias. Orlando, Florida: Grune and Straton, Inc.; 1985. p. 265-275.
13. Moe GKRW, Abildskov JA. A computer model of atrial fibrillation. American Heart Journal 1964;67:200–220. [PubMed: 14118488]
14. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med Sep 3;1998 339(10):659–666. [PubMed: 9725923]
15. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation Jan 18;2000 101(2):194–199. [PubMed: 10637208]
16. Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. Circulation Sep 22;1998 98(12):1236–1248. [PubMed: 9743516]
17. Boldt A, Wetzel U, Lauschke J, Weigl J, Gummert J, Hindricks G, Kottkamp H, Dhein S. Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. Heart Apr;2004 90(4):400–405. [PubMed: 15020515]
18. Luo MH, Li YS, Yang KP. Fibrosis of Collagen I and Remodeling of Connexin 43 in Atrial Myocardium of Patients with Atrial Fibrillation. Cardiology Sep 1;2006 107(4):248–253. [PubMed: 16953110]
19. Mariscalco G, Engstrom KG, Ferrarese S, Cozzi G, Bruno VD, Sessa F, Sala A. Relationship between atrial histopathology and atrial fibrillation after coronary bypass surgery. J Thorac Cardiovasc Surg Jun;2006 131(6):1364–1372. [PubMed: 16733171]
20. Nakai T, Chandy J, Nakai K, Bellows WH, Flachsbart K, Lee RJ, Leung JM. Histologic Assessment of Right Atrial Appendage Myocardium in Patients with Atrial Fibrillation after Coronary Artery Bypass Graft Surgery. Cardiology Sep 28;2006 108(2):90–96. [PubMed: 17008797]
21. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB, Kalman JM. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. Circulation Sep 23;2003 108(12):1461–1468. [PubMed: 12952837]

22. Cha TJ, Ehrlich JR, Zhang L, Nattel S. Atrial ionic remodeling induced by atrial tachycardia in the presence of congestive heart failure. Circulation Sep 21;2004 110(12):1520–1526. [PubMed: 15381657]

23. Cha TJ, Ehrlich JR, Zhang L, Shi YF, Tardif JC, Leung TK, Nattel S. Dissociation between ionic remodeling and ability to sustain atrial fibrillation during recovery from experimental congestive heart failure. Circulation Jan 27;2004 109(3):412–418. [PubMed: 14718405]

24. Shinagawa K, Shi YF, Tardif JC, Leung TK, Nattel S. Dynamic nature of atrial fibrillation substrate during development and reversal of heart failure in dogs. Circulation Jun 4;2002 105(22):2672–2678. [PubMed: 12045175]

25. Li D, Benardeau A, Nattel S. Contrasting efficacy of dofetilide in differing experimental models of atrial fibrillation. Circulation Jul 4;2000 102(1):104–112. [PubMed: 10880422]

26. Lee KW, Everett TH, Rahmutula D, Guerra JM, Wilson E, Ding C, Olgin J. Pirfenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. Circulation. 2006

27. Derakhchan K, Li D, Courtemanche M, Smith B, Brouillette J, Page PL, Nattel S. Method for simultaneous epicardial and endocardial mapping of in vivo canine heart: application to atrial conduction properties and arrhythmia mechanisms. J Cardiovasc Electrophysiol May;2001 12(5): 548–555. [PubMed: 11386516]

28. Stambler BS, Fenelon G, Shepard RK, Clemo HF, Guiraudon CM. Characterization of sustained atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure. J Cardiovasc Electrophysiol May;2003 14(5):499–507. [PubMed: 12776867]

29. Fenelon G, Shepard RK, Stambler BS. Focal origin of atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure. J Cardiovasc Electrophysiol Oct;2003 14(10):1093–1102. [PubMed: 14521664]

30. Ryu K, Shroff SC, Sahadevan J, Martovitz NL, Khrestian CM, Stambler BS. Mapping of atrial activation during sustained atrial fibrillation in dogs with rapid ventricular pacing induced heart failure: evidence for a role of driver regions. J Cardiovasc Electrophysiol Dec;2005 16(12):1348–1358. [PubMed: 16403068]

31. Everett TH, Wilson EE, Verheule S, Guerra JM, Foreman S, Olgin J. Structural Atrial Remodeling Alters the Substrate and Spatiotemporal Organization of AF: A Comparison in Canine Models of Structural and Electrical Atrial Remodeling. Am J Physiol Heart Circ Physiol. Jul 28;2006

32. Okuyama Y, Miyauchi Y, Park AM, Hamabe A, Zhou S, Hayashi H, Miyauchi M, Omichi C, Pak HN, Brodsky LA, Mandel WJ, Fishbein MC, Karagueuzian HS, Chen PS. High resolution mapping of the pulmonary vein and the vein of Marshall during induced atrial fibrillation and atrial tachycardia in a canine model of pacing-induced congestive heart failure. J Am Coll Cardiol Jul 16;2003 42(2): 348–360. [PubMed: 12875775]

33. Weber KT, Brilla CG, Janicki JS. Myocardial fibrosis: functional significance and regulatory factors. Cardiovasc Res Mar;1993 27(3):341–348. [PubMed: 8490934]

34. Hanatani A, Yoshiyama M, Kim S, Omura T, Toda I, Akioka K, Teragaki M, Takeuchi K, Iwao H, Takeda T. Inhibition by angiotensin II type 1 receptor antagonist of cardiac phenotypic modulation after myocardial infarction. J Mol Cell Cardiol Sep;1995 27(9):1905–1914. [PubMed: 8523451]

35. Urata H, Boehm KD, Philip A, Kinoshita A, Gabrovsek J, Bumpus FM, Husain A. Cellular localization and regional distribution of an angiotensin II-forming chymase in the heart. J Clin Invest Apr;1993 91(4):1269–1281. [PubMed: 7682566]

36. Xiao HD, Fuchs S, Campbell DJ, Lewis W, Dudley SC Jr, Kasi VS, Hoit BD, Keshelava G, Zhao H, Capecchi MR, Bernstein KE. Mice with cardiac-restricted angiotensin-converting enzyme (ACE) have atrial enlargement, cardiac arrhythmia, and sudden death. Am J Pathol Sep;2004 165(3):1019–1032. [PubMed: 15331425]

37. Shi Y, Li D, Tardif JC, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. Cardiovasc Res May;2002 54(2):456–461. [PubMed: 12062350]

38. Boldt A, Scholl A, Garbade J, Resetar ME, Mohr FW, Gummert JF, Dhein S. ACE-inhibitor treatment attenuates atrial structural remodeling in patients with lone chronic atrial fibrillation. Basic Res Cardiol May;2006 101(3):261–267. [PubMed: 16382287]

39. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol Jun 7;2005 45(11):1832–1839. [PubMed: 15936615]
40. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation Nov 20;2001 104(21):2608–2614. [PubMed: 11714658]
41. Sakabe M, Fujiki A, Nishida K, Sugao M, Nagasawa H, Tsuneda T, Mizumaki K, Inoue H. Enalapril prevents perpetuation of atrial fibrillation by suppressing atrial fibrosis and over-expression of connexin43 in a canine model of atrial pacing-induced left ventricular dysfunction. J Cardiovasc Pharmacol Jun;2004 43(6):851–859. [PubMed: 15167279]
42. Li Y, Li W, Yang B, Han W, Dong D, Xue J, Li B, Yang S, Sheng L. Effects of Cilazapril on atrial electrical, structural and functional remodeling in atrial fibrillation dogs. J Electrocardiol. Oct 24;2006
43. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol Jun 18;2003 41(12):2197–2204. [PubMed: 12821247]
44. Okazaki H, Minamino T, Tsukamoto O, Kim J, Okada K, Myoishi M, Wakeno M, Takashima S, Mochizuki N, Kitakaze M. Angiotensin II type 1 receptor blocker prevents atrial structural remodeling in rats with hypertension induced by chronic nitric oxide inhibition. Hypertens Res Apr; 2006 29(4):277–284. [PubMed: 16778335]
45. Goette A, Staack T, Rocken C, Arndt M, Geller JC, Huth C, Ansorge S, Klein HU, Lendeckel U. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. J Am Coll Cardiol May;2000 35(6):1669–1677. [PubMed: 10807475]
46. Boldt A, Scholl A, Garbade J, Resetar ME, Mohr FW, Gummert JF, Dhein S. ACE-inhibitor treatment attenuates atrial structural remodeling in patients with lone chronic atrial fibrillation. Basic Res Cardiol May;2006 101(3):261–267. [PubMed: 16382287]
47. Hirayama Y, Atarashi H, Kobayashi Y, Horie T, Iwasaki Y, Maruyama M, Miyauchi Y, Ohara T, Yashima M, Takano T. Angiotensin-converting enzyme inhibitor therapy inhibits the progression from paroxysmal atrial fibrillation to chronic atrial fibrillation. Circ J Jun;2005 69(6):671–676. [PubMed: 15914944]
48. L'Allier PL, Ducharme A, Keller PF, Yu H, Guertin MC, Tardif JC. Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. J Am Coll Cardiol Jul 7;2004 44(1):159–164. [PubMed: 15234426]
49. Murray KT, Rottman JN, Arbogast PG, Shemanski L, Primm RK, Campbell WB, Solomon AJ, Olgin JE, Wilson MJ, Dimarco JP, Beckman KJ, Dennish G, Naccarelli GV, Ray WA. Inhibition of angiotensin II signaling and recurrence of atrial fibrillation in AFFIRM. Heart Rhythm Dec;2004 1 (6):669–675. [PubMed: 15851238]
50. Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, Ducharme A. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation Jun 17;2003 107(23):2926–2931. [PubMed: 12771010]
51. Zaman AG, Kearney MT, Schecter C, Worthley SG, Nolan J. Angiotensin-converting enzyme inhibitors as adjunctive therapy in patients with persistent atrial fibrillation. Am Heart J May;2004 147(5):823–827. [PubMed: 15131537]
52. Van Noord T, Crijns HJ, van den Berg MP, Van Veldhuisen DJ, Van Gelder IC. Pretreatment with ACE inhibitors improves acute outcome of electrical cardioversion in patients with persistent atrial fibrillation. BMC Cardiovasc Disord Jan 24;2005 5(1):3. [PubMed: 15667649]
53. Pedersen OD, 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 Jul 27;1999 100(4):376–380. [PubMed: 10421597]
54. Lijnen PJ, Petrov VV, Fagard RH. Induction of cardiac fibrosis by transforming growth factor-beta (1). Mol Genet Metab Sep–Oct;2000 71(1–2):418–435. [PubMed: 11001836]

55. Iyer SN, Gurujeyalakshmi G, Giri SN. Effects of pirfenidone on transforming growth factor-beta gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. J Pharmacol Exp Ther Oct;1999 291(1):367–373. [PubMed: 10490926]

56. Garcia L, Hernandez I, Sandoval A, Salazar A, Garcia J, Vera J, Grijalva G, Muriel P, Margolin S, Armendariz-Borunda J. Pirfenidone effectively reverses experimental liver fibrosis. J Hepatol Dec; 2002 37(6):797–805. [PubMed: 12445421]

57. Shihab FS, Bennett WM, Yi H, Andoh TF. Pirfenidone treatment decreases transforming growth factor-beta1 and matrix proteins and ameliorates fibrosis in chronic cyclosporine nephrotoxicity. Am J Transplant Feb;2002 2(2):111–119. [PubMed: 12099512]

58. Shimizu T, Kuroda T, Hata S, Fukagawa M, Margolin SB, Kurokawa K. Pirfenidone improves renal function and fibrosis in the post-obstructed kidney. Kidney Int Jul;1998 54(1):99–109. [PubMed: 9648068]

59. Shimizu T, Fukagawa M, Kuroda T, Hata S, Iwasaki Y, Nemoto M, Shirai K, Yamauchi S, Margolin SB, Shimizu F, Kurokawa K. Pirfenidone prevents collagen accumulation in the remnant kidney in rats with partial nephrectomy. Kidney Int Suppl Dec;1997 63:S239–243. [PubMed: 9407470]

60. Saba S, Janczewski AM, Baker LC, Shusterman V, Gursoy EC, Feldman AM, Salama G, McTiernan CF, London B. Atrial contractile dysfunction, fibrosis, and arrhythmias in a mouse model of cardiomyopathy secondary to cardiac-specific overexpression of tumor necrosis factor-{alpha}. Am J Physiol Heart Circ Physiol Oct;2005 289(4):H1456–1467. [PubMed: 15923312]

61. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation Dec 11;2001 104(24):2886–2891. [PubMed: 11739301]

62. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. Circulation Dec 16;2003 108(24):3006–3010. [PubMed: 14623805]

63. Mihm MJ, Yu F, Carnes CA, Reiser PJ, McCarthy PM, Van Wagoner DR, Bauer JA. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. Circulation Jul 10;2001 104(2):174–180. [PubMed: 11447082]