

## Review Article

# Contribution of the Endothelin System to the Genesis and Maintenance of Atrial Fibrillation: Review of the Literature and Clinical Implications

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**T**he prevalence of atrial fibrillation (AF) in the developed world is around 1.5-2% and these figures are continuing to rise.<sup>1-3</sup> The risk of stroke in this group of patients is increased five-fold,<sup>3</sup> whereas the incidence of heart failure is threefold that of the general population. In addition, we should take into account the decrease in the quality of life of AF patients, which is attributable not only to the above-mentioned consequences of the arrhythmia, but also to the symptoms.<sup>4</sup> Feeling the irregular rhythm is the major symptom in AF patients and is the main reason that these patients seek medical advice. In the treatment of AF, maintenance of sinus rhythm seems to play a pivotal role. Many antiarrhythmic agents have been validated for cardioversion or prevention of recurrences, while various surgical techniques have also been widely used.<sup>5</sup> Ablation techniques using either radiofrequency energy or cryoballoon have been widely applied during the past few years.<sup>6,7</sup>

Nevertheless, all of these approaches to the management of AF have failed to prove their absolute efficacy. The AF recurrence rate after ablation is still 30% or higher.<sup>2,8</sup> There is considerable concern nowadays about the factors that contrib-

ute to recurrences of AF and many hypotheses have been proposed concerning the mechanisms involved.<sup>2,4,9</sup>

## ET-1 and the cardiovascular system

Endothelin-1 (ET-1), discovered in 1988 by Yanagisawa et al,<sup>10</sup> is a 21 amino acid peptide with a potent vasoconstrictor action that participates in both the physiological function of the cardiovascular system and cardiovascular disease. Although endothelium is the main source of ET-1, it is also produced in vascular smooth muscle cells, cardiomyocytes, fibroblasts, macrophages and leucocytes.<sup>11</sup> ET-1 is the eventual product of a gene on chromosome 6 that encodes preproET-1 protein. This is converted to proET-1 on secretion into the cytoplasm, which itself undergoes enzymatic cleavage by an endopeptidase to form big ET-1. ET-1 is generated from big ET-1 by endothelin-converting enzymes and is secreted predominantly into the vessel wall.<sup>11</sup>

Many factors contribute to the production of ET-1. Physico-chemical stimuli, such as hypoxia or shear stress, hormones such as adrenaline or angiotensin II, blood components such as thrombin, are only a few of the stimuli that promote ET-1 syn-

thesis in the human body. Conversely, nitric oxide or prostacyclin inhibit its production.<sup>11</sup>

The downstream effects of ET-1 are mediated by two distinct receptor subtypes, ETA and ETB. Endothelin receptors are expressed in a variety of human tissues. In human heart, cardiomyocytes and fibroblasts predominantly express ETA, although ETB expression is more abundant in cardiac conducting tissue.<sup>12</sup>

From an early stage, it was proposed that ET-1 might contribute to the development of cardiovascular disease. As previously described,<sup>13</sup> a role for ET-1 might be inferred on the basis of one or, preferably, a combination of three conditions: (1) production of ET-1 or actions at its receptors are altered; (2) administration of ET-1 recapitulates features of the disease; and (3) compounds that reduce ET activity reduce the signs of the disease. On this basis, a role for ET-1 has been suggested in a variety of cardiovascular diseases, predominantly through chronic (for example, hypertension, ischaemic heart disease and congestive heart failure) or acute (acute myocardial infarction) conditions. Apart from its strong vasoconstrictive action, ET-1 seems to have direct electrophysiological properties.<sup>14</sup>

The mechanisms of ET-1-induced arrhythmias are not completely understood. Three-dimensional mapping has revealed that ET-1-induced arrhythmias could be attributed to multi- or monofocal activity.<sup>15</sup> Action potential duration increase and early afterdepolarisation have also been observed during ET-1 administration, suggesting that triggered activity is the most likely mechanism. Micro-re-entry mechanisms could also participate in the genesis of arrhythmias due to ET-1, as dispersion of repolarisation and regional heterogeneity seem to play a part.<sup>16</sup>

On the other hand Udyavar et al<sup>16</sup> reported that ET-1 may have an antiarrhythmic potential through its direct electrophysiological effects on the pulmonary vein cardiomyocytes and its action on multiple ionic currents, by shortening action potential duration and by decreasing pulmonary vein firing rates.

### ET-1 and AF

Although the mechanisms of AF are not fully understood, it is well accepted that its development requires both a trigger and a susceptible substrate. Triggered focal activity from pulmonary veins is considered as the main cause of AF, whereas micro-re-entry mechanisms are involved in the maintenance of the irregular rhythm.<sup>17</sup>

Atrial remodelling reflects a spectrum of pathophysiological changes. These changes include alterations at the levels of ionic channels, cellular energy imbalance, neurohormonal expression, inflammatory responses, and physiological adaptations. The duration of AF has also been directly associated with structural alterations in the left atrium (LA), including fibrosis, inflammation and a significant increase in size.

Guazzi et al<sup>18</sup> reported that endothelial dysfunction (ED) increases oxidative stress and pro-inflammatory agents, and impairs nitric oxide (NO)-dependent vasorelaxation. AF is a risk factor for ED as documented by (1) impaired acetylcholine-mediated blood flow increase; (2) reduced plasma nitrate levels; (3) additive impairment of flow-mediated dilatation by comorbidities causing ED, and (4) efficacy of cardioversion. Several possible mechanisms sustain the AF-ED association:

- a. An impaired rheology. Endothelial NO release is tightly regulated by laminar shear stress and AF induces a turbulent flow that may impair arterial vessel distension and responsiveness. Specifically,  $Ca^{++}$  elicits NO synthase (eNOS) activation, and shear stress application to endothelial cells increases intracellular  $Ca^{++}$ , primarily in response to regular pulsatile flow at a rate higher than that observed in the presence of oscillatory pulsatile flow.
- b. The atrium's activity on arterial vessels. The left atrium produces NO and may serve as an endocrine organ releasing nitroso compounds. A disorganised atrial contraction markedly reduces eNOS expression.
- c. AF induces atrial inflammation and elevation of C-reactive protein and cytokines, exerting a pro-inflammatory activity on endothelial cells.
- d. Systemic factors such as the renin-angiotensin system (RAS) may be prominent. In fact, RAS and inflammation reciprocally "cross-talk". Angiotensin II increases atrial cell death and the RAS contributes to myocardial and vascular oxidative stress in AF. RAS inhibition prevents AF. Important clinical correlates of ED in AF patients are muscle under-perfusion, premature lactic acidosis and ergoreflex over-signalling during physical activity.

Atrial fibrosis is a common finding in patients with AF.<sup>19</sup> Fibrosis may result from pathologies such as cardiac dysfunction, mitral valvular disease, and myocardial ischemia, and atrial fibroblast function

has been the focus of studies investigating the mechanisms of AF. AF is associated with increased levels of angiotensin-converting enzyme (ACE) and activation of angiotensin II (ANG II)-regulated intracellular signalling pathways, while ACE inhibitors have been found beneficial in reducing the frequency of AF.<sup>20</sup> In addition, AF is also associated with increased atrial mRNA levels of ET-1.<sup>21</sup> In the left ventricle, ET-1 augments left ventricular contractile function and activates hypertrophic signalling pathways.<sup>22,23</sup> In fact, the signalling mechanisms regulating hypertrophic response in ventricular cardiomyocytes have been studied extensively, but the signalling mechanisms involved in stress response in atrial myocardium are not well understood. There is some evidence, however, suggesting that signalling mechanisms activated by cardiomyocyte stretch or by neurohumoral agonists may differ between the atrial and ventricular cardiomyocytes.

Beat-to-beat variation in blood flow dynamics during AF has also been associated with evidence of endothelial dysfunction. Skolidis et al<sup>24</sup> aimed to confirm that endothelial dysfunction is present in patients with AF and to test the hypothesis that endothelial dysfunction is reversible upon restoration of normal sinus rhythm and correction of blood flow dynamics. Therefore, they measured the endothelium-dependent (flow-mediated dilation [FMD]) and endothelium-independent (nitroglycerin-mediated dilation [NMD]) vasodilator function of the brachial artery in patients who were in AF, and compared the results with those 24 hours and 1 month after successful restoration by electrical cardioversion and maintenance of sinus rhythm. Compared with control subjects, patients showed lower FMD during AF and similar NMD. Patients in whom sinus rhythm was restored and sustained at both 24 hours and 1 month showed increased FMD. The authors concluded that AF is associated with an impairment of endothelial function that improves after sinus rhythm restoration. Shin et al<sup>25</sup> reported that AF subjects had significantly impaired FMD, which could be reversed through the restoration of sinus rhythm by successful catheter ablation. Baseline FMD, high sensitivity C-reactive protein, and left atrial volume were important predictors for AF recurrence after catheter ablation.

Endothelin plays a crucial role in endothelial function. Whether the restoration of sinus rhythm can reverse endothelial dysfunction associated with AF remains doubtful. Wozakowska-Kaplon et al<sup>26</sup> studied patients with persistent AF, normal left ven-

tricular systolic function, and no symptoms of heart failure. They concluded that, in this subgroup of patients, persistent AF does not lead to an increase in ET-1 plasma concentrations compared to patients in sinus rhythm. The recovery of sinus rhythm following electrical cardioversion in patients with persistent AF does not lead to a significant decrease in ET-1 plasma concentration. Therefore, plasma ET-1 concentration does not seem to be a predictor of the maintenance of sinus rhythm for 30 days after successful cardioversion.

The widely held view on the arrhythmogenic properties of ET-1 has been challenged by data concerning the electrophysiological effects of ET-1 on the atrial and ventricular myocardium.<sup>27,28</sup> In the setting of myocardial ischaemia, the findings of Sharif et al<sup>28</sup> suggested a dual (both pro- and antiarrhythmic) action of ET-1. In their experiments, endogenously released ET-1, acting via both receptors, produced a proarrhythmic effect, while low dose ET-1, administered exogenously, was antiarrhythmic.

In addition, there is evidence from *in vivo* and *in vitro* studies suggesting that the stretch-induced early activation of brain natriuretic peptide gene expression in rat atrial myocytes, but not in ventricular myocytes, is mediated via an ET-1 dependent mechanism.<sup>29,30</sup> In the heart, ET-1 acts as a chronotropic and inotropic agent, constricting arteries and inducing myocardial cell hypertrophy.<sup>14</sup> The mixed ET-A/B receptor antagonist bosentan is in clinical use for the treatment of pulmonary artery hypertension. Bosentan treatment not only induces vasodilation and decreases pulmonary vascular resistance, but also lowers the mean right atrial pressure.<sup>14</sup> It was recently reported that mechanical stretch induces an increase in ET-1 gene expression, which suggests an interaction between them.

Kerkela et al<sup>31</sup> found that *in vitro* mRNA levels of ETA receptor and endothelin-converting enzyme-1 were significantly higher in atrial tissue compared with ventricular tissue. This suggests that ET-1 plays a central role in the regulation of atrial stretch response. In addition, members of the ET-1 signalling system are expressed at higher levels in atrial compared with ventricular myocardium, which may be relevant in cardiovascular conditions that increase the atrial load.

In contrast, there are other reports suggesting that the expression of ETA receptor in the atria of patients who developed AF after cardiac surgery was down-regulated significantly compared to those with

preserved sinus rhythm.<sup>32</sup> These results are in concordance with previous findings<sup>33,34</sup> and may allow the generation of hypotheses concerning the underlying electrophysiological mechanisms of AF. It may be postulated that, under certain circumstances, ET-1 exerts antiarrhythmic actions in the atria,<sup>35</sup> an effect that is lost after a decrease in ETA receptors. This hypothesis is further supported by previous findings in isolated human atrial cells, where isoproterenol prolonged the action potential duration and produced arrhythmic depolarisations; both effects were prevented by ET-1, independently of beta-blocker treatment.<sup>32</sup> Thus, the antiarrhythmic potential of ET-1 in human atria in the setting of hypercatecholaminemia, such as post-surgery, may explain these findings.

An alternative hypothesis was proposed by Boyden, who suggested that the electrophysiological properties of ET-1 in human atria are mediated by neither ETA nor ETB receptors.<sup>36</sup> This assumption is based on the fact that, despite the reported down-regulation of both receptors, functional data are absent.<sup>33</sup> In particular, there are no solid data available to indicate a pathophysiological link between the function of the remaining receptors and abnormal calcium handling, leading to the initiation of AF.

Wang et al<sup>37</sup> reported that plasma levels of big ET-1 before ablation were related to AF recurrence during long-term follow up and were a strong predictor of recurrence only in patients with paroxysmal AF. In addition, plasma levels of big ET-1 correlated well with left atrial dimensions. Furthermore, the sinus rhythm maintenance rate was lower in patients with high big ET-1 levels than in patients with low levels. This might be due to the fact that, along with many other neuroendocrine factors participating in left atrial remodelling – such as brain natriuretic peptide, ANG II, aldosterone, growth factors, and sympathetic high tension – the endothelin system may be involved in this process. Down-regulation of ET-A and ET-B receptor protein levels from paroxysmal AF to persistent AF suggest that its role might differ in the distinct forms of AF.<sup>32</sup>

Cardiac fibroblasts respond to growth factors, such as ET-1, and are an important source of ET-1 in the heart. In fact, there is evidence that a hypertrophic response to ANG II in isolated cardiomyocytes is mediated by local production of ET-1.<sup>38</sup> The importance of understanding the role of ET-1 in atrial myocardium is emphasised by the fact that there are a number of novel compounds in development that target ET-1 signalling.<sup>7</sup> Recent data suggest that the

effect of ET antagonists on the development of atrial hypertrophy, a known risk factor for AF, should be further investigated.

Mayyas et al<sup>21</sup> have shown that increased levels of ET-1 in the left atrial appendage are associated with and may contribute to increased AF persistence and left atrial dilatation. These data suggest that both ET-1 gene expression and processing are activated during AF. ET-1, in turn, enhances the expression of genes involved in cardiac dilatation, hypertrophy, and fibrosis. The combined influence of these factors may contribute to the impact of ET-1 on AF persistence. This study suggests that increased expression of atrial ET-1 is associated with the progression of atrial dysfunction. Thus, interventions that decrease atrial ET-1 expression or block its receptors might be useful in slowing the progression of AF.

### Therapeutic implications

Pharmacological strategies for treating AF are frequently directed at rhythm control and are mostly ineffective. ET-1 signalling may be a target for AF-focused therapeutic interventions.

Circumferential pulmonary vein ablation is an effective strategy for paroxysmal AF since it mainly targets AF-triggering pulmonary veins, but it is less effective on an AF substrate compared with persistent AF. Therefore, in the case of a modified substrate, such as left atrial structural and electrical remodelling, left atrial and systemic neuroendocrine adaptive changes might play a more important role in persistent AF. All the above factors are causes of AF recurrence after ablation.<sup>38</sup>

Ablation techniques have been more efficacious than antiarrhythmic drugs in preventing recurrences in the setting of paroxysmal AF.<sup>39</sup> Moreover, the above-mentioned studies raise the hypothesis that ablation techniques should be implemented at an early stage of the disease in order to attenuate electrical and structural remodelling. A study by Erdei et al<sup>40</sup> was the first in which left atrial structural and functional remodelling were examined in detail in patients who had cryoballoon catheter ablation for paroxysmal AF. Successful ablation prevented progressive left atrial remodelling, whereas the left atrium was enlarged in patients with recurrent atrial arrhythmias.<sup>41</sup> Indeed, Ciconte et al<sup>6</sup> concluded, based on multivariate analysis, that only persistent AF duration and relapses during the blanking period independently predicted arrhythmia recurrences.

Consequently, the type of AF seems to be of importance. Indeed, a recent meta-analysis showed that ablation techniques are more efficacious in paroxysmal than in other forms of AF. Consequently, less “diseased” patients are more likely to be cured by means of ablation, indicating that the evolution of the substrate in AF needs to be interrupted.<sup>41</sup>

The recently published DECAAF study (Delayed Enhancement-MRI determinant of successful Catheter Ablation of Atrial Fibrillation) showed that the stage of atrial fibrosis prior to ablation is a new and powerful independent predictor of outcomes.<sup>42</sup> Multivariate analysis revealed that two independent predictors of successful ablation or recurrent symptoms were the stage of atrial fibrosis before ablation and the residual fibrosis after. For every percentage point increase in fibrosis before ablation, there was a 6.3% increased risk of recurrent symptoms after ablation.

The type of the intervention applied, i.e. radiofrequency ablation or cryoballoon, might also be of importance. Radiofrequency ablation creates more extensive fibrosis than cryoballoon; thus, it may trigger a neurohormonal cascade that might lead to structural remodelling. However, Mugnai et al<sup>7</sup> did not find any clinical predictors to predict AF recurrences. Over a medium-term follow up, conventional point-by-point radiofrequency ablation and cryoballoon ablation showed similar success rates. Ciconte et al<sup>6</sup> confirmed that the ablative strategy as index procedure did not show any effect in predicting arrhythmic recurrences.

Thus, a considerable rate of AF recurrence is one of the major limitations of pulmonary vein isolation. ET-1 is involved in atrial remodelling. Nazagawa et al<sup>43</sup> proved that, among various biomarkers, only levels of ET-1 before pulmonary vein isolation were significantly higher in the recurrence group compared with the non-recurrence group. Both mean left atrial pressure and diastolic blood pressure were significantly higher in the recurrence group than in the non-recurrence group. The plasma ET-1 level and mean left atrial pressure were correlated. Multiple logistic regression analyses showed that higher levels of plasma ET-1 and diastolic blood pressure were significant predictors of AF recurrence three to six months after pulmonary vein isolation. These findings suggest that the plasma ET-1 level before pulmonary vein isolation could be a crucial index of AF recurrence.

To conclude, ET-1 appears to be an important component in the pathogenesis of AF. Nevertheless, further research is warranted to elucidate the patho-

physiological significance of ET-1 and its receptors in the genesis of AF and the possible predictive and therapeutic value.

## References

1. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012; 33: 2719-2747.
2. Renoux C, Patenaude V, Suissa S. Incidence, mortality, and sex differences of non-valvular atrial fibrillation: a population-based study. *J Am Heart Assoc*. 2014; 3: e001402.
3. Andrikopoulos G, Pastromas S, Mantas I, et al. Management of atrial fibrillation in Greece: the MANAGE-AF study. *Hellenic J Cardiol*. 2014; 55: 281-287.
4. Tsounis D, Ioannidis A, Bouras G, et al. Assessment of health-related quality of life in a greek symptomatic population with atrial fibrillation: correlation with functional status and echocardiographic indices. *Hellenic J Cardiol*. 2014; 55: 475-485.
5. Fragakis N, Katritsis DG. Surgical treatment for atrial fibrillation: where do we stand? *Hellenic J Cardiol*. 2012; 53: 210-216.
6. Ciconte G, Ottaviano L, de Asmundis C et al. Pulmonary vein isolation as index procedure for persistent atrial fibrillation: One-year clinical outcome after ablation using the second-generation cryoballoon. *Heart Rhythm*. 2015; 12: 60-66.
7. Mugnai G, Chierchia GB, de Asmundis C, et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. *Am J Cardiol*. 2014; 113: 1509-1513.
8. Liu J, Fang PH, Hou Y, et al. The value of transtelephonic electrocardiogram monitoring system during the “Blanking Period” after ablation of atrial fibrillation. *J Electrocardiol*. 2010; 43: 667-672.
9. Giallafos I, Triposkiadis F, Oikonomou E, et al. Incident atrial fibrillation in systemic sclerosis: the predictive role of B-type natriuretic peptide. *Hellenic J Cardiol*. 2014; 55: 313-321.
10. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*. 1988; 332: 411-415.
11. Kirkby NS, Hadoke PW, Bagnall AJ, Webb DJ. The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? *Br J Pharmacol*. 2008; 153: 1105-1119.
12. Molenaar P, O'Reilly G, Sharkey A, et al. Characterization and localization of endothelin receptor subtypes in the human atrioventricular conducting system and myocardium. *Circ Res*. 1993; 72: 526-538.
13. Gray GA, Webb DJ. The endothelin system and its potential as a therapeutic target in cardiovascular disease. *Pharmacol Ther*. 1996; 72: 109-148.
14. Yorikane R, Koike H, Miyake S. Electrophysiological effects of endothelin-1 on canine myocardial cells. *J Cardiovasc Pharmacol*. 1991; 17 Suppl 7: S159-162.
15. Duru F, Barton M, Lüscher TF, Candinas R. Endothelin and cardiac arrhythmias: do endothelin antagonists have a thera-

- peutic potential as antiarrhythmic drugs? *Cardiovasc Res.* 2001; 49: 272-280.
16. Udyavar AR, Chen YC, Chen YJ, Cheng CC, Lin CI, Chen SA. Endothelin-1 modulates the arrhythmogenic activity of pulmonary veins. *J Cardiovasc Electrophysiol.* 2008; 19: 285-292.
  17. Haïssaguerre M, Jaos P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998; 339: 659-666.
  18. Guazzi M, Arena R. Endothelial dysfunction and pathophysiological correlates in atrial fibrillation. *Heart.* 2009; 95: 102-106.
  19. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol.* 2008; 51: 802-809.
  20. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. *Lancet.* 2007; 369: 1208-1219.
  21. Mayyas F, Niebauer M, Zurick A, et al. Association of left atrial endothelin-1 with atrial rhythm, size, and fibrosis in patients with structural heart disease. *Circ Arrhythm Electrophysiol.* 2010; 3: 369-379.
  22. Sugden PH. An overview of endothelin signaling in the cardiac myocyte. *J Mol Cell Cardiol.* 2003; 35: 871-886.
  23. Szokodi I, Kerkelä R, Kubin AM, et al. Functionally opposing roles of extracellular signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase in the regulation of cardiac contractility. *Circulation.* 2008; 118: 1651-1658.
  24. Skolidis EI, Zacharis EA, Tsetis DK, et al. Endothelial cell function during atrial fibrillation and after restoration of sinus rhythm. *Am J Cardiol.* 2007; 99: 1258-1262.
  25. Shin SY, Na JO, Lim HE, et al. Improved endothelial function in patients with atrial fibrillation through maintenance of sinus rhythm by successful catheter ablation. *J Cardiovasc Electrophysiol.* 2011; 22: 376-382.
  26. Wozakowska-Kapłon B, Bartkowiak R, Janiszewska G, Grabowska U. Does atrial fibrillation affect plasma endothelin level? *Cardiol J.* 2010; 17: 471-476.
  27. Burrell KM, Molenaar P, Dawson PJ, Kaumann AJ. Contractile and arrhythmic effects of endothelin receptor agonists in human heart in vitro: Blockade with SB 209670. *J Pharmacol Exp Ther.* 2000; 292: 449-459.
  28. Sharif I, Kane KA, Wainwright CL. Endothelin and ischaemic arrhythmias-antiarrhythmic or arrhythmogenic? *Cardiovasc Res.* 1998; 39: 625-632.
  29. Magga J, Vuolteenaho O, Marttila M, Ruskoaho H. Endothelin-1 is involved in stretch-induced early activation of B-type natriuretic peptide gene expression in atrial but not in ventricular myocytes: acute effects of mixed ET(A)/ET(B) and AT1 receptor antagonists in vivo and in vitro. *Circulation.* 1997; 96: 3053-3062.
  30. Thibault G, Doubell AF, Garcia R, Larivière R, Schiffrin EL. Endothelin-stimulated secretion of natriuretic peptides by rat atrial myocytes is mediated by endothelin A receptors. *Circ Res.* 1994; 74: 460-470.
  31. Kerkelä R, Ilves M, Pikkarainen S et al. Key roles of endothelin-1 and p38 MAPK in the regulation of atrial stretch response. *Am J Physiol Regul Integr Comp Physiol.* 2011; 300: R140-149.
  32. Kolettis TM, Kyriakides ZS, Zygaki E, et al. Endothelin system and atrial fibrillation post-cardiac surgery. *J Interv Card Electrophysiol.* 2008; 21: 203-208.
  33. Brundel BJ, Van Gelder IC, Tuinenburg AE, et al. Endothelin system in human persistent and paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol.* 2001; 12: 737-742.
  34. Saygili E, Rana OR, Günzel C, et al. Rate and irregularity of electrical activation during atrial fibrillation affect myocardial NGF expression via different signalling routes. *Cell Signal.* 2012; 24: 99-105.
  35. Redpath CJ, Rankin AC, Kane KA, Workman AJ. Anti-adrenergic effects of endothelin on human atrial action potentials are potentially anti-arrhythmic. *J Mol Cell Cardiol.* 2006; 40: 717-724.
  36. Boyden PA. Endothelin: AF-riend or AF-oe. *J Cardiovasc Electrophysiol.* 2001; 12: 743
  37. Wang H, Liu J, Fang P, et al. Big endothelin-1 as a predictor of atrial fibrillation recurrence after primary ablation only in patients with paroxysmal atrial fibrillation. *Herz.* 2012; 37: 919-925.
  38. Ito H, Hirata Y, Adachi S, et al. Endothelin-1 is an autocrine/paracrine factor in the mechanism of angiotensin II-induced hypertrophy in cultured rat cardiomyocytes. *J Clin Invest.* 1993; 92: 398-403.
  39. Wilber DJ, Pappone C, Neuzil P, et al; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA.* 2010; 303: 333-340.
  40. Erdei T, Dénes M, Kardos A, et al. Could successful cryoballoon ablation of paroxysmal atrial fibrillation prevent progressive left atrial remodeling? *Cardiovasc Ultrasound.* 2012; 10: 11.
  41. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc.* 2013; 2: e004549.
  42. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA.* 2014; 311: 498-506.
  43. Nakazawa Y, Ashihara T, Tsutamoto T, Ito M, Horie M. Endothelin-1 as a predictor of atrial fibrillation recurrence after pulmonary vein isolation. *Heart Rhythm.* 2009; 6: 725-730.