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Reverse atrial electrical remodeling: A systematic review

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Abstract

Atrial remodeling is a term introduced in 1995 to describe alterations in atrial structure or function. Atrial electrical remodeling is characterized by a reduction of refractory period and action potential duration, dispersion in refractoriness, and a reduction in conduction velocity of impulse propagation. Numerous animal and human studies have demonstrated that atrial electrical remodeling impairs normal atrial conduction and provides an environment for ectopic and re-entrant activity, thus creating a substrate for the initiation or maintenance of atrial fibrillation. Interestingly, atrial electrical remodeling has been shown to be reversible. In this systematic review, we examine the occurrence of reverse atrial electrical remodeling in various clinical settings. (Cardiol J 2011; 18, 6: 625–631)

Key words: atrial electrical remodeling, electrical remodeling

Introduction to atrial remodeling

Atrial remodeling is a term used to describe the phenomenon of persistent alterations in the properties or functions of atrial tissue. The concept of atrial remodeling was introduced as early as 1995 by Wijffels et al. [1], who demonstrated that atrial fibrillation (AF) in goats induces atrial functional alterations that favour the maintenance of AF. As they put it: "Atrial fibrillation begets atrial fibrillation." Atrial remodeling has significantly enhanced our understanding of the pathophysiology implicated in atrial arrhythmias. Altered atrial structure or function increases the likelihood of ectopic and re-entrant activity [2, 3], thus providing a substrate for the development of arrhythmias. The role of atrial remodeling specifically in AF has received increasing attention in recent literature. The rapid atrial rates in AF have been shown in a canine model to induce an abbreviation of atrial effective refractory period (ERP) and action potential duration (APD), subsequently favoring the initiation or maintenance of AF [4].

On the other hand, congestive heart failure (CHF) promotes AF through a different paradigm — atrial structural remodeling. An earlier study by Li et al. [5] in a canine model of CHF reported unchanged ERP and suggested the promotion of AF primarily through the disruption of atrial conduction by interstitial fibrosis.

Reduced atrial contractility, the development of fibrosis, and atrial enlargement are the key characteristics of atrial structural remodeling. Patients with chronic AF demonstrate a reduction of ~75%

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in the contractile force of their right atrial appendages compared to those without AF [6, 7], which may result from the loss of sarcomeres or reduced Ca^{2+} release from the sarcoplasmic reticulum [3]. Furthermore, transgenic mice with cardiac-restricted overexpression of angiotensin-converting enzyme [8] or transforming growth factor-beta1 (TGF-β1) [9] have shown increased atrial fibrosis and AF propensity, highlighting the pathophysiological importance of angiotensin-II and TGF-β1. In addition to the changes on a microscopic level, echocardiography in a canine model revealed biatrial enlargement after rapid atrial pacing for six weeks [4]. An increased atrial size is able to accommodate more re-entry circuits and is an important clinical predictor for AF development and maintenance [10], as well as AF recurrence following catheter ablation [11] or cardioversion [12]. In the presence of CHF, interstitial fibrosis is apparently the most important phenomenon which interferes with local atrial conduction by interrupting the arrangement of cardiomyocytes. While a canine model of CHF has shown interstitial fibrosis to be associated with increased conduction heterogeneity [5], impaired conduction and increased susceptibility to AF have also been documented in CHF patients [13]. Upon recovery from CHF in the canine model, fibrosis and conduction abnormalities did not reverse, and a substrate for AF remained despite the reversal of electrical remodeling, suggesting that structural remodeling is an important contributor to the AF substrate in CHF [14]. Although seemingly detrimental, structural remodeling may in fact be an adaptive response to the underlying cardiac disease.

Atrial electrical remodeling in AF is best represented by the shortening of atrial ERP and the loss of rate adaptation [1, 4], but also includes spatial heterogeneity of atrial refractoriness and conduction velocity [1, 15, 16]. The concept of atrial electrical remodeling was first introduced by Wijffels et al. [1] and Morillo et al. [4] in 1995, who concomitantly demonstrated a shortening of atrial ERP in goats with sustained AF and dogs with rapid atrial pacing, respectively. Increases in P-wave duration, dispersion in refractoriness, and vulnerability to AF were also observed [4]. Refractory period abbreviation is attributable to the down-regulation of L-type Ca^{2+} current (I_{CaL}) as a result of Ca^{2+} accumulation within atrial myocytes due to rapid atrial activation [17, 18]. The abbreviation in refractory periods shortens the wavelengths of atrial impulse, favoring the occurrence of multiple wavelet re-entry and subsequently increasing the susceptibility to AF or stability of AF [3, 19]. Increased dispersion of atrial refractoriness has been documented in paroxysmal AF patients [21] and patients with early postoperative-AF after coronary artery bypass grafting [22] and is associated with their AF inducibility. Interestingly, electrical remodeling that promotes AF in the presence of CHF is markedly different: prolonged P-wave duration and ERP, and unchanged rate adaptation [23].

The fundamental basis of electrical remodeling is the alteration in the expressions or activity of ion channels — ionic remodeling. Reduction in I_{CaL}, reportedly as much as 70% in atrial myocytes of AF patients [17], is an important contributor to the abbreviation of APD and atrial refractoriness [17, 18, 20]. The down-regulation of I_{CaL} is to prevent Ca^{2+} overload during rapid atrial rate where the Ca^{2+} concentration in atrial myocytes is substantially increased [2]. Studies have also reported reduced transient outward current (I_{to}) in both canine [20] and human [17] models of AF, and increased background inward rectifier (I_{K1}) [17, 24]; their clinical relevance remains unclear however. A concomitant decrease in sodium current (I_{Na}) and conduction velocity in a canine model of rapid atrial pacing suggested a potential role for I_{Na} in the development of an AF substrate [15]. Interestingly, I_{Na} was reportedly unchanged in humans with AF compared to those in sinus rhythm [17]. A handful of studies have consistently demonstrated an upregulation of a constitutively active form of acetylcholine-dependent potassium current (I_{KACh}) both in canine and human myocytes of AF and may be involved in ERP abbreviation [17, 25]. Connexins are important in impulse propagation and their roles in AF have been inconsistent in studies. Elvan et al. [26] reported an increase in connexin43 protein expression in dogs with AF, while Van der Welden et al. [27] found instead a heterogeneously decreased atrial connexin40 distribution in goat models. Although the upregulation of both connexin40 and connexin43 have been observed in the left atrium (LA) tissue of AF patients, their effects on atrial impulse propagation remain to be elucidated [28].

A handful of studies have investigated autonomic remodeling in canine models of AF. Studies using positron emission tomography imaging [29] and immunocytochemical staining [30] have consistently reported an increased atrial sympathetic nerve innervation as well as an inhomogeneous sympathetic innervation in paced dogs compared to controls.

Atrial remodeling is not a permanent event and has been shown to be reversible. We conducted this systematic review to put together the cohort stu-

dies relevant to reverse atrial electrical remodeling. To the best of our knowledge, there has been no previous systematic review discussing or comparing reverse atrial electrical remodeling reported in various clinical scenarios. We aim to determine the conditions under which reverse atrial electrical remodeling occurs, and its clinical manifestation.

Methods

We performed a systematic search of literature published on Pubmed and EMBASE database in English from 1990 up to May 2011, including both animal and human studies. The terms used for the search were: "atrial remodeling", "atrial electrical remodeling", "reverse atrial remodeling", and "reverse remodeling". Two reviewers (HP and AB) independently screened titles to identify studies relevant to the topic. Disagreement was solved by consensus.

Methods to quantify atrial electrical remodeling and reverse electrical remodeling

Non-invasive method

Maximum P-wave duration, P-wave dispersion, and the newly emerged high-resolution signal-averaged P-wave (SAPW) assessed using a surface electrocardiogram are widely accepted non-invasive markers for atrial electrical remodeling. Atrial conduction disturbances are manifested as a prolongation of P-wave duration. Previously, specific atrial electrophysiological variables such as atrial ERP and conduction velocity of atrial impulse could only be assessed by invasive study. It was not until recently that SAPW analysis was recognized as a non-invasive tool to provide information on atrial electrophysiology. Redfearn et al. [31] were the first to correlate surface P-wave parameters and atrial electrophysiology parameters, and acknowledged the usefulness of SAPW as an evaluation tool for atrial electrophysiology.

Invasive method

Electrophysiology study is an invasive method to determine atrial ERP, conduction velocity of atrial impulse, and vulnerability to AF. Wijffels et al. [1] and Morillo et al. [4] were the first to demonstrate atrial electrical remodeling after rapid atrial pacing in goat and canine models, respectively. The goats were instrumented with multiple electrodes at the epicardium of both atria connected to an external pacemaker; the dogs were paced at 400 bpm for six weeks using a transvenous lead sutured to the right atrial appendage. Atrial ERP was determined using an internal catheter to introduce extrastimuli at decreasing coupling intervals until it failed to result in atrial depolarization. Atrial vulnerability to AF was assessed in both studies by stimulating the heart with either multiple extrastimuli or a single stimulus of four times the threshold.

Results

Our search returned 5,212 articles that were potentially useful, and ten titles were found relevant to the purpose of the study after careful screening. Only studies that assessed atrial electrical remodeling before and after intervention were included. Searching the references of the ten articles provided another three manuscripts for this review.

Post-cardioversion

We identified five prospective studies that evaluated reverse atrial electrical remodeling post-cardioversion in patients with AF. Two studies that measured the SAPW duration at one month [32] and three months [33] post-cardioversion consistently reported a significant decrease in those who remained in sinus rhythm, but not in those who recurred. The study by Chalfoun et al. [32] showed a decrease in SAPW from 159 ± 19 to 146 ± 17 ms ($p < 0.0001$) in 22 patients at one month, while Healey et al. [33] reported a shortening from 158 ± 28 to 152 ± 24 ms ($p = 0.009$) in 44 patients, but not in the 32 who recurred (164 ± 31 to 158 ± ± 36 ms, $p = 0.3$). Furthermore, a study by Guo et al. [34] reported shorter P-wave duration in patients who remained in sinus rhythm within six months post-cardioversion compared to those with AF recurrence (143 ± 17 *vs* 157 ± 24 ms, $p < 0.0001$). Two other studies performed electrophysiologic testing post-cardioversion and concomitantly reported prolonged atrial ERP at the distal coronary sinus at four days [35] and one week [36] ($p < 0.01$). Consistent with other studies, the latter group also found a significant decrease of SAPW duration at one week (135 ± 18 to 129 ± 13 ms, $p = 0.04$) [36]. The shortening of SAPW duration and prolongation of atrial ERP represent faster intra-atrial conduction and provide clear evidence for reverse atrial electrical remodeling.

Post-ablation

Atrial fibrillation ablation has also been demonstrated to be effective in reversing atrial remodeling. In a recent study by Tops et al. [37], 112 pa-

roxysmal AF and 36 persistent AF patients who had catheter ablation showed a decrease in maximum LA volume (30 ± 7 to 25 ± 7 mL/m^2, p < 0.001) and an increase in LA total emptying fraction (41 ± 13 to 45 ± 14%, p = 0.002). Those who showed > 15% decrease in maximal LA volume were classified as responders; they demonstrated significant increases in LA emptying fraction and LA maximal strain after the ablation. In contrast, the non-responders showed no changes in LA volume, emptying fraction, or strain. The recurrences of AF in responders and non-responders were 12% and 69% (p < 0.001), respectively. These findings illustrate the reversal of atrial remodeling, represented by an improved LA transport and contractile function. Interestingly, the LA strain was significantly lower at baseline in the non-responders, suggesting that the strain may be a reflection of structural changes that can indicate the reversibility of LA remodeling by catheter ablation. In an earlier study, AF patients who remained in sinus rhythm after the ablation showed a significant improvement in LA emptying fraction (25 ± 13.1 to 30.8 ± 7.9%, p = 0.03) and contractility, and a concomitant decrease in LA minimal volume (44.7 ± ± 14.9 to 38.0 ± 11.5 mL/m^2, p = 0.04) [38]. These parameters were unchanged from baseline for those with AF recurrence. This is consistent with another study which also reported a reduction in LA size only in those successfully restored to sinus rhythm after linear ablation (48.6 ± 7.6 to 44.8 ± 4.7 mm, p = 0.0001), but an increase in others (48.2 ± 8.1 to 52.3 ± 7.8 mm, p = 0.001) [39]. A comparison of reverse atrial remodeling in catheter ablation and electrical cardioversion was conducted by Choi et al. [40]. They found that both atrial defibrillation methods resulted in a significant reduction in LA size at three months. However, improvement in LA function at three months, represented by LA ejection fraction, was observed after cardioversion (31.4 ± 9.5 to 39.5 ± 9.1%, p = 0.004), but not after ablation (31.8 ± 12.8 to 30.9 ± 10%, p = 0.64).

Post-cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT), also known as biventricular pacing, is the optimal treatment for patients with advanced heart failure. Yu et al. [41] reported an improved atrial contractile function and compliance in a study of 107 heart failure patients who received CRT for three months. Only those defined as responders, who demonstrated a reduction of left ventricular end-systolic volume of > 10% after CRT, showed an improvement in LA wall contraction velocity (3.6 ± 1.8 to 4.5 ± ± 1.9 cm/s *vs* 3.2 ± 1.8 to 3.5 ± 1.9 cm/s, p = 0.01) and atrial compliance, as determined by tissue Doppler velocity and strain imaging. Furthermore, responders reported an increase in LA emptying fraction and a decrease in LA size that were not observed in the non-responders. This is consistent with another study by Donal et al. [42], who also reported decreased LA volume (45.5 ± 8.5 to 39.1 ± 9.6 mL/m^2, p < 0.001) and increased LA emptying fraction in responders after six months of CRT.

Post-mitral commissurotomy

We found one study, by John et al. [43], reporting significant reverse atrial electrical remodeling in patients with mitral stenosis after mitral commissurotomy. Patients presented a decrease in LA volume and mean LA pressure accompanied by a shortening of P-wave duration (139 ± 19 to 135 ± ± 20 ms, p = 0.047). At long-term follow-up, a reduction in atrial ERP at cycle lengths of 600 ms (p < 0.0001) and 400 ms (p = 0.0001) and further shortening of P-wave duration to 113 ± 19 ms (p = = 0.04) were demonstrated. Most importantly, a trend for reduced vulnerability for AF was shown by a decrease in the number of patients with sustained AF. These findings suggest that reverse atrial electrical remodeling may be induced by the removal of chronic stretch in patients with mitral stenosis.

Post-continous positive airway pressure in obstructive sleep apnea patients

Previously, our group reported an increase in maximum P-wave duration of 7.6 ms and P-wave dispersion (14.6 ± 7.5 *vs* 8.9 ± 3.1 ms, p < 0.001) in moderate-severe obstructive sleep apnea (OSA) patients compared to controls, illustrating atrial electrical remodeling associated with the disease [44]. No studies have assessed the potential of continuous positive airway pressure (CPAP) treatment to reverse these changes. However, our group recently found a shortening of SAPW duration from 131.9 ± 10.4 ms to 126.2 ± 8.8 ms (p < 0.001) after four to six weeks of CPAP in 19 severe OSA patients, an indication of improved atrial conduction and reverse electrical remodeling [45].

Discussion

Since its introduction in 1995, numerous studies in animal and human models have emerged to characterize atrial electrical remodeling. The findings have contributed significantly to our under-

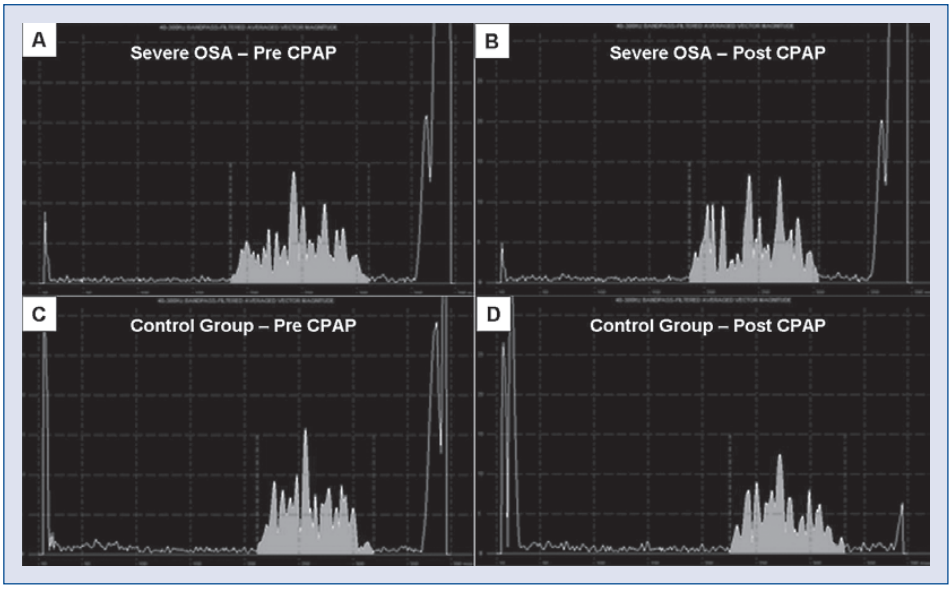

Figure 1A–D. Sample signal average P-wave (SAPW) analyses for a severe obstructive sleep apnea (OSA) subject (upper panels) and a control subject (lower panels). At first (left) and second (right) SAPW recording; x-axis — [ms]; y-axis — [μV]. The area in gray represents the average P-wave of 100 beats. There is a reduction of SAPW duration after four to six weeks of continuous positive airway pressure (CPAP) in the subject with severe OSA, but no change in SPAW duration in the control case.

standing of the pathophysiology underlying the initiation and maintenance of AF.

While reverse structural remodeling has been extensively studied, evidence on reverse electrical remodeling is currently limited. We were only able to identify a handful of relevant studies. Nonetheless, they concomitantly showed that reverse atrial electrical remodeling is manifested as reduced SAPW or P-wave duration, prolonged atrial ERP, and reduced vulnerability to AF, often accompanied by reduced LA size and improved LA function.

In the setting of post-cardioversion for AF, the current literature consistently reports a prolongation of atrial ERP and shortening of P-wave duration only in those who remain in sinus rhythm, not in those who recur. Reductions of as much as 6 ms by one week [36] and 13 ms by one month [32] have been reported. Interestingly, reverse electrical remodeling was not observed in those who recurred, highlighting the relationship between reverse remodeling and AF recurrence.

In post-ablation, studies concurrently reported significant improvement in LA emptying fraction and reduction in LA size, only in those successfully restored to sinus rhythm. The improvement in atrial conduction post-ablation may improve atrial function, subsequently contributing to the maintenance of sinus rhythm.

Studies on post-cardioversion and post-ablation suggest that reverse atrial electrical remodeling occurs only in successfully defibrillated patients, and that improvements in atrial conduction and atrial function are related. It has been suggested that a certain amount of reverse atrial electrical remodeling must occur to sufficiently prevent the recurrence of AF. However, it remains unclear whether reverse remodeling is the cause or the consequence of the maintenance of sinus rhythm.

A couple of studies have shown that CRT in heart failure patients improved atrial contractile function and LA emptying fraction. Changes in P-wave duration or atrial ERP, if any, have yet to be systematically investigated. The enhanced LA function may be the consequence of improved atrial conduction allowing better co-ordination of atrial cardiomyocytes. But this interpretation requires further prospective studies.

The only study of mitral commissurotomy in patients with mitral stenosis reported reduced P-wave duration and AF propensity, further strengthening the relationship between atrial remodeling and vulnerability to AF.

Our group has shown a reduction in SAPW duration in patients with severe OSA treated with CPAP (Fig. 1). The resolution of intermittent hypoxemia and hypercapnia may remove the triggers

that cause atrial electrical remodeling, thereby improving atrial conduction. There was a positive correlation between the reduction of the apnea/hypopnea index and the shortening of the SAPW. These findings also suggest that the underlying disease may need to be targeted to reverse atrial electrical remodeling.

Conclusions

The concept of reverse atrial electrical remodeling is intriguing. A full understanding of it holds the prospect of tremendous clinical value in reducing the morbidity associated with AF. Further studies of reverse atrial electrical remodeling consisting of larger populations in different clinical scenarios are warranted. The findings will shed light on determining the best treatment option for patients at risk of AF.

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