行政院國家科學委員會專題研究計畫 成果報告

Enalapril 對長期心房纖維顫動病人於心律復整術後對竇房結功能不全之助益

研究成果報告(精簡版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 96-2314-B-040-025-
執 行 期 間 ：96 年 08 月 01 日至 97 年 07 月 31 日
執 行 單 位 ：中山醫學大學醫學系

計 畫 主 持 人：翁國昌

計畫參與人員：此計畫無其他參與人員：翁國昌

處 理 方 式 ：本計畫可公開查詢

中 華 民 國 97 年 10 月 29 日

Enalapril Facilitates the Reversal of Sinus Node Remodeling Following Cardioversion of Long-Standing Atrial Fibrillation

Kwo-Chang Ueng, MD, PhD; Hui-Ling Chiou, PhD; Chung-Sheng Lin, MD, PhD; Chung-Yin Chen, MD, PhD; [§§]Shih-Ann Chen, MD.

Division of Cardiology; Institute of Medicine; School of Medical Laboratory and Biotechnology, Chung Shan Medical University, and Chung Shan Medical University Hospital, Taiwan. [§§]National Yang-Ming University, School of Medicine and Taipei Veterans General Hospital, Taiwan.

Address for correspondence:

Kwo-Chang Ueng, MD, PhD

Cardiovascular Study Group, Institute of Medicine; Division of Cardiology, Chung Shan Medical University Hospital, 110, Sec.1, Jian-Guo N. Rd., Taichung City, 402, Taiwan.

Fax: + 886 4 2252 3626 Telephone: + 886 2 2532603

E-mail: ueng.kc@msa.hinet.net

Background—To date the mechanisms of atrial fibrillation -associated sinus node dysfunction have not been fully elucidated. Normal cardiac pacemaker activity is widely distributed in the right atrium. Enalapril has been reported to attenuate atrial fibrosis and structural remodeling.

Methods and Results— 40 patients with chronic atrial fibrillation > 3 months referred for electrical cardioversion were pretreated with either placebo (group I, n = 20) or enalapril 10 mg twice daily for 4 weeks (group II, n = 20) prior to cardioversion. Immediately following successful cardioversion to sinus rhythm, corrected sinus node recovery time (CSNRT) and sinus cycle length (SCL) were measured. In group I, CSNRT and SCL were significantly shorter in group II than in group I ($P < 0.05$).

Conclusions: Depressed sinus node function is observed after conversion of chronic atrial fibrillation. Chronic atrial fibrillation impaired sinus node function. Pretreatment of enalapril improved such functions.

Key Words: atrium; fibrillation; remodeling; sinus node

Introduction

The frequent association of atrial fibrillation (AF) with sinus node dysfunction (SND) has long been recognized ( ). However, to date the mechanisms of AF-associated SND have not been fully elucidated. The sinoatrial node (SAN) is conventionally considered to be located at the base of the superior vena cava (SVC). Detailed animal and human mapping has demonstrated that normal cardiac pacemaker activity is widely distributed in the right atrium. In the human atrium, the pacemaker complex extends for up to 75 mm along the long axis of the sulcus terminalis and precaval band. Recently atrial activation maps by Boineau JP. revealed that the sinus pacemaker activity could arise from an extensive structure along the long axis of the crista terminalis (CT) from the superior to the inferior vena cava (IVC) in humans. Several lines of evidence demonstrated that anatomic and structural changes along the CT have been implicated in a reduction in functional sinus node reserve in patients with sick sinus syndrome and congestive heart failure. In addition, extensive modification ablation of the sinus node targeting this structure has been established as a treatment for inappropriate sinus tachycardia. Thus, the CT is believed to be an important anatomic structure in the initiation and propagation of sinus impulse. Previous studies in AF-induced SND have focused on the electrophysiological parameters such as sinus node recovery time (SNRT) and/or SACT, but have not characterized the electrophysiology of this structure in this condition. In the present study, we evaluated the detailed electrophysiological and electroanatomic changes in the sinus pacemaker complex and, in particular, conduction

properties of the CT in patients with AF by electrophysiological and non-contact mapping studies performed after electrocardioversion and compared these changes with those in age-matched control subjects without history of AF.

Methods

Patient Population

The study group consisted of 40 patients with chronic lone AF who were referred for electrical cardioversion. These patients with chronic AF lasting > 3 months by serial electrocardiograms (ECG). They were all free from structural heart disease or hyperthyroidism, as assessed by transthoracic echocardiography, coronary angiography and thyroid function test. Those patients on amiodarone therapy in the preceding 3 months, with a mean ventricular rate < 40 beats/minute or a history of sick sinus syndrome were excluded. No patients in this study had pacemakers or defibrillators implanted. All study patients with AF received oral anticoagulation at a dosage adjusted to achieve an international normalized ratio of 2 or more for at least four weeks before the electrocardioversion. For study group (group I, n=20) , enalapril 10 mg was administered at twice daily and could be increased to 20 mg twice daily in patients with hypertension. Another age- and sex-matched 20 patients received placebo, served as control group (group II). Electrical cardioversion was scheduled after 4 weeks of randomization. Left atrial diameter, right atrial area, and left ventricular

ejection fraction were assessed by transthoracic echocardiography in all subjects according to standard method. All patients provided written informed consent to participate in the research study, and the study protocol was approved by our Research and Ethics Committee.

Cardioversion Protocol

All AF patients were studied in the postabsorptive state, and all antiarrhythmic drugs were discontinued for >5 half-lives before the procedure. Details of the electrical cardioversion have been described previously. Briefly, after obtaining a 12-lead ECG and measurement of arterial pressure, the patients were attached to an external defibrillator (CodeMaster XL+, Hewlett-Packard). Then, the patients were adequately anesthetized with propofol (1.5 mg/kg, i.v.), and a direct current shock synchronized to the R wave was delivered. The location of the paddle was oriented in the apex-sternum direction and shocks started with 200 J of stored energy followed by 300 J and then twice with 360 J until the restoration of SR.

Electrophysiology Study

All AF patients entered the electrophysiologic study immediately after successful cardioversion. After right femoral and right internal jugular venous access was obtained, the following electrophysiology catheters were inserted: (1) a decapolar catheter was positioned in the coronary sinus (CS) with the proximal electrode pair at the ostium. (2) a 20-pole deflectable “halo” catheter introduced via a long vascular sheath and positioned along the

long axis of the CT with bipole 1/2 cranial and bipole 19/20 caudal. Bipole 3/4 was positioned at the junction of the SVC and right atrium, as previously described. (3) Another quadripolar electrode catheter was positioned at the high lateral right atrium (HRA). A 9-French sheath placed in the left femoral vein was used to introduce the noncontact mapping catheter. The orifices of SVC, IVC and coronary sinus were identified by venograms. Stability of the electrode catheters was maintained by fluoroscopic monitoring.

Surface ECG and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier recorder system (CardioLab System, Prucka Engineering, Inc) with optical disk storage for offline analysis. Intracardiac electrograms were filtered from 30 to 500 Hz and measured with computer-assisted calipers at a sweep speed of 100 or 200 mm/s. The pulmonary capillary wedge pressure, the pulmonary artery pressure, and the right atrial pressure were also measured during a right heart catheterization.

Sinoatrial Nodal Function

Sinoatrial nodal function was evaluated by determination of sinoatrial conduction time (SACT) and corrected sinus node recovery time (CSNRT). The corrected sinus node recovery time (CSNRT) was assessed at CLs of 600, 500 and 400 ms after a 60-second pacing train at twice the diastolic threshold. Pacing was performed from the HRA, repeated twice at each CL and averaged. A CSNRT > 525 ms was deemed as sinus node dysfunction. The longest time

interval from the last paced atrial depolarization to the first spontaneous sinus cycle was recorded as the $SNRT_{max}$. $CSNRT_{max}$ was determined by subtracting the mean SCL measured before the beginning of atrial pacing from the $SNRT_{max}$.

Sinus Pacemaker Location and Pacemaker Shift

The site of the sinus pacemaker complex along the CT was defined by the bipole demonstrating the earliest activity during SR and for the first sinus beat after a 30-second pacing train at a CL of 600 ms. For the purposes of evaluating the sinus pacemaker shift along the CT, we defined the presence of different ($\geqq 2$) earliest dipole of the CT catheter. The number of sinus pacemaker shift was calculated for 2 minutes during stable SR in each patient.

Statistical Analysis

All variables were expressed as mean±SD. All values are expressed as means ± SD. Differences between the groups were evaluated using an unpaired Student's *t*-test. Correlation coefficients were calculated by the Spearman rank method. The association of sinus node function (CSNRT/SACT) with other measured parameters was assessed by the Spearman correlation test. A value of $P < 0.05$ was considered to be statistically significant.

Results

Patient Characteristics

The electrophysiological evaluation was completed successfully in all control subjects. Overall group characteristics and hemodynamic data are shown in Table 1. There were 26 men and 14 women (67±12 years; range 40 to 69). As shown in Table 1, group I patients with AF did not differ from control subjects with SR with respect to clinical parameters. The median duration of AF before attempted cardioversion was 14 months (range, 4 to 60).

AERP

At all sites and at all CLs evaluated, there was a shorter ERP in group I patient than in controls (Figure 1). This reached statistical significance at the high CT at 600 ms ($P<0.01$), 500 ms ($P<0.01$), and 400 ms ($P<0.01$); mid CT at 600 ms ($P<0.01$), 500 ms ($P<0.01$), and 400 ms ($P<0.01$); low CT at 600 ms ($P<0.01$) and 500 ms ($P<0.01$); His bundle area at 600 ms ($P<0.05$); and proximal CS at 500 ms, distal CS at 600 ms ($P<0.01$). There was no significant difference in the heterogeneity of atrial ERP. Dispersion of AERP at the high CT and mid CT (215±18 and 213±23 ms) was significantly longer at any of 3 pacing CLs than that at the low CT, proximal and distal CS (193±23 and 198±21 ms) ($P<0.05$).

Corrected Sinus Node Recovery Time

The corrected sinus node recovery time was < 525 ms in all control subjects whereas the CSNRT was over 525 msec in 16 patients (2/3) with AF. The corrected sinus node recovery

time was significantly longer at each CL evaluated in group I patients compared with age-matched control subjects ($P<0.0001$): at a CL of 600 ms, 363±84 versus 237±81 ms ($P<0.01$); at a CL of 500 ms, 422±96 versus 256±80 ms ($P<0.01$); and at a CL of 400 ms, 426±112 versus 277±87 ms ($P<0.01$).

Sinus Pacemaker Location

During SR, the earliest site of activation along the CT was located significantly more caudally along this structure in group I patients compared with age-matched control subjects (bipole 4.7±2.4 versus 2.4±2.2; $P=0.03$). After overdrive suppression, the return of sinus activity was also observed to originate from a significantly more caudal sinus pacemaker site along the CT in group I patients compared with controls ($P=0.002$): After pacing at a CL of 600 ms, earliest activity returned at bipole 9.3±0.5 versus 6.5±2.6 ($P<0.01$); at a CL of 500 ms, at bipole 9.2±0.9 versus 6.8±2.3 ($P<0.01$); and at a CL of 400 ms, at bipole 9.1±0.9 versus 6.9±2.4 ($P<0.01$).

Discussion

Major findings

The present study is, to the best of our knowledge, the first to demonstrate that long-standing AF results in structural change with evidence of loss of voltage amplitude in the superior and

middle region of the crista terminalis, an anatomically more localized (caldaulized) sinus node complex, and also an abnormal, circuitous propagation of sinus activity around this structure, clinically manifested as with significant prolongation of the SACT and CSNRT, possibly indicating an abnormality in both the impulse generation and conducting impulses out of this structure in this clinical setting. These abnormal processes at CT may be, at least partly, responsible for the genesis of SND observed in patients undergoing electrocardioversion of persistent AF. An important finding is that patients with AF demonstrated an anatomically more localized sinus node complex with significant prolongation of the intrinsic sinus CL and CSNRT, which were improved with enalapril therapy.

SND and Atrial Electrical Remodeling in Chronic AF

Many studies have shown that persistent rapid atrial rates are accompanied with the prolongation of sinus node recovery time in animal and human studies, and this phenomenon reversed gradually with maintenance of sinus rhythm. Recently, Hadian et al. have demonstrated sinus node remodeling with prolongation of sinoatrial conduction time and corrected sinus node recovery time even after a brief episode (10 to 15 minutes) of rapid atrial pacing in humans. These authors suggest that electrical remodeling secondary to short-term AF is responsible for the genesis of this phenomenon. The primary pathophysiology is presumed to be the extension of the atrial electrical remodeling to this structure. Our previous

work demonstrated that complete reversal of atrial electrical remodeling following cardioversion of chronic AF in humans happened on the third day after cardioversion. These SND changes partially reversed toward baseline 1 week after conversion to sinus rhythm in 2 to 6 weeks of rapid atrial pacing canine model. However, previous clinical observation has demonstrated that the persistence of SND after cardioversion continues to exist within 3 to 7 days after complete reversal of electrical remodeling. Furthermore, the time course of SND (cSNRT) recovery was much slower than that of AERP reversal, with significant regional heterogeneity, in the AF group when compared with the SR group. In accordance with other studies, atrial ERPs were significantly shorter in our patients converted from chronic AF compared with those in the SR group. The range of relative refractoriness was equally shortened in patients with and without SND during HRA stimulation. Also, there was no difference in the range of relative refractoriness and ERP heterogeneity (transcristal conduction properties) of all sites from patients with SND compared with those without SND. Furthermore, no significant correlation could be demonstrated between CSNRT and/or SACT and regional ERPs or CoV-ERP in either group. Given the fact that atrial tissue is different electrophysiologically from the sinus node and longer durations of AF, extrapolation of findings from atrial electrical remodeling studies might be not appropriate. Our observations suggest the existence of site-dependent shortening and dispersion of refractoriness appears to be a common property of the trial myocardium and does not necessarily forecast SND in this

condition. Therefore, development of SND following chronic AF must also depend on a 'second factor' other than extension of atrial electrical remodeling since the persistence of SND continues after recovery of atrial electrical remodeling has been completed.

SND and Structural Remodeling of the Sinus Node Complex in AF

In fact, histopathological studies demonstrated that persistent AF is associated with significant damage to the sinus node and the perinodal tissue. Interestingly, patients with asynchronous ventricular pacing, atrial septal defects, or congestive heart failure—conditions known to be associated with the development of AF—demonstrate evidence of sinus node (structural) remodeling. Recent studies in patients with significant atrial septal defects or asynchronous ventricular pacing, conditions known to be associated with the development of AF, have also observed sinus node remodeling with prolongation of the CSNRT. Sanders P et al. demonstrates that patients with CHF have significant sinus node remodeling characterized by anatomic and structural changes along the crista terminalis with a reduction in functional sinus node reserve. In the present study in patients with AF and no prior sick sinus syndrome, we observed not only evidence of sinus node dysfunction but also structural change along the crista terminalis that resulted in abnormal conduction at this structure. In present study, AF patients had a significantly longer CSNRT and SACT compared with controls, indicating an abnormality in both the impulse generation in the sinus nodal complex and conducting impulses out of the sinus node in persistent AF. It was speculated that chronic AF would

result in electrophysiologic and structural remodeling of the sinus pacemaker complex, clinically manifested as sinus node dysfunction. Our results indicated the complexity of the sinus node remodeling process in relation not only to electrical remodeling but also to structural remodeling and CT involvement.

Previous Studies of Sinus Node Abnormalities in AF

In addition to the presence of widespread abnormalities of conduction, significant functional conduction delay at the anatomic region of the high CT was observed. Although the role of these conduction abnormalities at the CT in the development of SND was not studied, it has been shown that the CT plays an important role in the development of typical atrial flutter Recent study demonstrates that patients with CHF have significant sinus node remodeling characterized by anatomic and structural changes along the crista terminalis with a reduction in functional sinus node reserve. Furthermore, possibly even more important, structural abnormalities due to AF causes sinus node dysfunction. It thus appears that structural remodeling secondary to AF is not confined to the atrial myocardium but also involves the sinus pacemaker complex.

Structural Remodeling of the Sinus Node Complex in AF

Histopathological studies demonstrated that persistent AF is associated with significant damage to the sinus node, the perinodal tissue and the sinus node artery. Given the widely

distributed nature of this complex extending from SVC-RA to along with CT, chronic AF-associated widespread atrial structural changes with involvement of this structure would lead to derangements of sinus node function. Interestingly, patients with asynchronous ventricular pacing, atrial septal defects, or congestive heart failure—conditions known to be associated with the development of AF—demonstrate evidence of sinus node remodeling. Further, altered nodal geometry resulting from excessive fibrosis or impaired intercellular coupling during AF may alter the direction of impulse transmission and its safety factor for conduction, thereby diminishing the ability of a small nodal source to drive a relatively large atrial mass after conversion to sinus rhythm.

Conclusion and Clinical Implication

These findings provide insights into mechanisms for SND secondary to long-standing AF. The present study indicated that sinus node function was disturbed in patients with AF, and may be related to structural remodeling rather than electrical remodeling in long-lasting AF. Structural remodeling is not a status limited to the atrial myocardium; it may also involve the sinus node complex. We have extended these observations by showing that SND following cardioversion of chronic AF, so that it is quite possible that the structural remodeling of the atria extends to the sinus node as well, resulting in sinus node dysfunction. Enalapril has been shown to prevent AF-induced interstitial fibrosis in the sinus node area and to improve sinus

node function in this pilot study, indicating the important role of structural changes of sinus node in the regulation of sinus node function. This possibility supporting therapeutic interventions using RAS inhibitors forms an attractive theoretical basis for interventions to reverse SND in such patients.

Acknowledgments

This study was supported by an intramural grant from the National Science Council, Taiwan (NSC 96-2314-B-040 -025), Taiwan.

References:

Boineau JP, Canavan TE, Schuessler RB, Cain ME, Corr PB, Cox JL. Demonstration of a widely distributed atrial pacemaker complex in the human heart. Circulation. 1988 Jun;77(6):1221-37.

Dobrzynski H, Li J, Tellez J, Greener ID, Nikolski VP, Wright SE, Parson SH, Jones SA, Lancaster MK, Yamamoto M, Honjo H, Takagishi Y, Kodama I, Efimov IR, Billeter R, Boyett MR. Computer three-dimensional reconstruction of the sinoatrial node. Circulation. 2005;111(7):846-54.

Kumagai K, Akimitsu S, Kawahira K, Kawanami F, Yamanouchi Y, Hiroki T, Arakawa K: Electrophysiological properties in chronic lone atrial . brillation. Circulation 1991;84:1662-1668.

Luck JC, Engel TR: Dispersion of atrial refractoriness in patients with sinus node dysfunction. Circulation 1979;60:404-412.

Poty H, Saoudi N, Haissaguerre M, Daou A, Clementy J, Letac B. Radiofrequency catheter ablation of atrial tachycardias. Am Heart J 1996;131:481–9.

Kalman JM, Olgin JE, Karch MR, Hamdan M, Lee RJ, Lesh MD. "Cristal tachycardias": origin of right atrial tachycardias from the crista terminalis identified by intracardiac echocardiography. J Am Coll Cardiol 1998;31:451–9.

Morton JB, Sanders P, Das A, Vohra JK, Sparks PB, Kalman JM. Focal atrial

tachycardia arising from the tricuspid annulus: electrophysiologic and electrocardiographic characteristics. J Cardiovasc Electrophysiol 2001;12:653–9.

Mallavarapu C, Schwartzman D, Callans DJ, Gottlieb CD, Marchlinski FE. Radiofrequency catheter ablation of atrial tachycardia with unusual left atrial sites of origin: report of two cases. Pacing Clin Electrophysiol 1996;19:988–92.

Deen VR, Morton JB, Vohra JK, Kalman JM. Pulmonary vein paced activation sequence mapping: comparison with activation sequences during onset of focal atrial fibrillation. J Cardiovasc Electrophysiol 2002;13:101–7.

Tang CW, Scheinman MM, Van Hare GF, et al. Use of P wave configuration during atrial tachycardia to predict site of origin. J Am Coll Cardiol 1995;26:1315–24.

Yamane T, Shah DC, Peng JT, et al. Morphological characteristics of P waves during selective pulmonary vein pacing. J Am Coll Cardiol 2001;38:1505–10.

Marrouche NF, Sippens Groenewegen A, Yang Y, Dibs S, Scheinman MM. Clinical and electrophysiologic characteristics of left septal atrial tachycardia. J Am Coll Cardiol 2002;40:1133–9.

McGuire MA, de Bakker JM, Vermeulen JT, et al. Atrioventricular junctional tissue. Discrepancy between histological and electrophysiological characteristics. Circulation 1996;94:571–7.

Wit AL, Fenoglio JJ, Jr., Wagner BM, Bassett AL. Electrophysiological properties of

cardiac muscle in the anterior mitral valve leaflet and the adjacent atrium in the dog. Possible implications for the genesis of atrial dysrhythmias. Circ Res 1973;32:731–45.