An Anatomical Approach to Determine the Location of the Sinoatrial Node During Catheter Ablation

Keiko Shimamoto, MD[a,b]; Kenichiro Yamagata, MD, PhD[a]; Kenzaburo Nakajima, MD[a]; Tsukasa Kamakura, MD, PhD[a], Mitsuru Wada, MD[a]; Yuko Inoue, MD, PhD[a]; Koji Miyamoto, MD, PhD[a]; Takashi Noda, MD, PhD[a]; Satoshi Nagase, MD, PhD[a]; Kengo F. Kusano MD, PhD[a]

[a]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka 564-8565, Japan

[b]Department of Molecular Imaging in Cardiovascular Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871, Japan

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests:

The authors have no conflicts of interest to disclose.

Corresponding Author:

Dr. Kenichiro Yamagata

Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center,

6-1, Kishibe-shimmachi, Suita, Osaka 564-8565, Japan

Tel: +81-6-6170-1070; Fax: +81-6-6833-9865

Email: look.tky@ncvc.go.jp

Reprint requests: None

Abstract

Introduction: The sinoatrial node (SAN) should be identified before superior vena cava (SVC) isolation to avoid SAN injury. However, its location cannot be identified without restoring sinus rhythm. This study evaluated the usefulness of the anatomically defined SAN by comparing it with the electrically confirmed SAN (e-SAN) and aimed to establish a safe and more efficient anatomical reference for SVC isolation than the previously reported reference of the roof of the right superior pulmonary vein (RSPV roof).

Methods and Results: The e-SAN was identified as the earliest activation site in the electro-anatomical map obtained during sinus rhythm. The anatomically defined SAN, the cranial edge of the crista terminalis (CT) visualized with intracardiac echocardiography (CT top), and the RSPV roof were tagged on one map. The distance from the e-SAN to each reference was measured. Among 81 patients, the height of the e-SAN from the CT top was −3.5 ± 10.3 mm. The e-SAN existed below 10 mm above the CT top in 78 (96%) patients and below the RSPV roof in 77 (95%) patients. A longer SVC sleeve was measured from 10 mm above the CT top compared to the RSPV roof (28.7 ± 11.2 vs. 22.5 ± 11.3 mm, $p < 0.001$). Faster heart rate predicted an e-SAN location higher than the CT top (adjusted OR [95% CI]; per 10 bpm increase: 1.6 [1.15–

2.22], p <0.01).

Conclusion: The CT top is useful in predicting the upper limit of the e-SAN and can provide a useful reference for SVC isolation.

Keywords: catheter ablation; echocardiography; intracardiac imaging techniques; sinus node; superior vena cava

Introduction

The superior vena cava (SVC) is one of the most common sites of atrial fibrillation (AF) associated with a non-pulmonary vein (PV) origin, and SVC isolation is essential procedure during ablation to control AF in up to 6-12% of the patients with AF[1-3]. SVC isolation is usually performed close to the SVC-right atrium (RA) junction, which is close to the sinoatrial node (SAN) cell complex; hence, SAN injury is a well-known complication of this procedure[4]. The electrically confirmed SAN (e-SAN), which is regarded as the earliest atrial activation site during sinus rhythm, can be used as a landmark during SVC isolation to avoid this injury. However, e-SAN cannot be always detected before the isolation of the SVC[1, 2, 5]. Hence, an anatomical landmark indicating the location of the e-SAN can be a useful guide during SVC isolation procedures in these patients.

Histologically, SAN cells are organized as complex crescent-shaped cells located at the superior border of the RA and extend parallel to the crista terminalis (CT)[6]. This complex has been reported to extend 1.0–3.5 mm into the SVC without distinctive variations in humans[6, 7]. Therefore, we set the highest point of the CT visualized by intracardiac echography (ICE) (CT top) as a reference point to locate the anatomically defined SAN because the highest point of the SAN complex is believed to

be located close to the top of the CT.

This study aimed to evaluate the usefulness of the CT top as a reference point to locate the e-SAN and to propose a new reference point based on the CT top that can be used during SVC isolation, by comparing this reference point with the roof of the right superior pulmonary vein (RSPV). The roof of the RSPV is close to the bottom of the right pulmonary artery (RPA), which has been reported as a landmark during SVC isolation[8].

Methods

Patients

This retrospective study enrolled 81 consecutive patients who underwent e-SAN mapping during catheter ablation at the National Cerebral and Cardiovascular Center, Japan, between April 2019 and June 2020. Patients with atrial pacing and patients who had a history of SVC isolation were excluded. The clinical and background data of the patients were obtained from their medical charts.

All subjects provided written informed consent before undergoing the ablation procedure, and the institutional review board of the National Cerebral and Cardiovascular Center approved this retrospective analysis of the patients clinically acquired data (M26-148-8).

Procedures

All patients were sedated with propofol and dexmedetomidine. The electrophysiological study was performed using the CARTO3 three-dimensional electroanatomical mapping (EAM) system (Biosense Webster, Diamond Bar, CA). Mapping information was obtained using a multipolar mapping catheter (PentaRay®; Biosense Webster). The activation map of the RA during sinus rhythm was recorded. The fast anatomical map (FAM) was also used to record anatomical details of the SVC, RA, left atrium (LA), and PVs. The cranial edge of the CT adjacent to the right atrial appendage was tagged on the EAM by navigating the ablation catheter (Smart Touch Surround Flow®; Biosense Webster) under two-dimensional ICE guidance (ACUSON AcuNav™ or SOUNDSTAR®; Biosense Webster). This geometrical point was defined as the CT top (Figure 1A). During determination process of the CT top, the activation map was hidden to blind the physician from the information of the e-SAN.

The bottom line of the RPA is one of the recommended landmarks used in SVC isolation; it is anatomically located just above the RSPV. Hence, we also marked the intersection of the middle line of the SVC and the roof of the RSPV (RSPV roof) on the FAM (Figure 1B, right).

SVC isolation is performed in patients in whom the SVC is suspected to be a non-PV focus of AF. Mapping of the e-SAN is usually performed before SVC isolation if the patient is in sinus rhythm. In our study, the level of the CT top and the RSPV roof were concealed during SVC isolation as the physician isolated the SVC based on the location of the e-SAN (at least > 5 mm above), or based on the particular line determined based on the shape of the anatomical FAM by the physician. Radiofrequency energy, of up to 35 W, was delivered point-by-point, with a target temperature of ≤ 37 °C along with 17–30 mL/min of saline irrigation. The phrenic nerve was placed above the isolation line during ablation to avoid phrenic nerve injury.

Measurements

All measurements were performed on the images created by CARTO3. The e-SAN, the CT top, and the RSPV roof were tagged on the FAM of the LA, and PVs were co-displayed on the same screen without tilting. A grid scale was used as a reference for distance, and the grid size of each square was configured to 10 mm. The relative height of the e-SAN from the CT top and the RSPV roof on the craniocaudal axis were measured (Figure 1C). Additionally, the SVC sleeve lengths, from the e-SAN, the CT top, and the RSPV roof to the highest point of the SVC, defined as voltage > 0.5

millivolts in this study, were measured in all patients. Furthermore, the SVC ablation height from each point was also measured in those who underwent SVC isolation.

We set a new SVC isolation reference based on the CT top which assured an equal safety level in terms of avoiding SAN injury to the RSPV roof and compared the characteristics of this point (Figure 1B, left).

[insert Figure1]

Statistical analysis

Quantitative variables are expressed as mean ± standard deviation. Student's t-test was used to compare the means of continuous variables. Categorical variables were presented as number (n) and percentage (%). Odds ratio (OR) with 95% confidence interval (CI) was estimated by univariate and multivariate logistic regression analyses, adjusted for age and sex, to evaluate predictive factors that identified patients who had higher e-SAN locations than the CT top. In each analysis, a two-sided significance level of 0.05 was considered statistically significant. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[9, 10].

Data Availability

The dataset from this study is held securely by the National Cerebral and Cardiovascular Center and is available from the corresponding author on reasonable request.

Results

Baseline characteristics

Patients' baseline characteristics are summarized in Table 1. Of the 81 patients, 52 (64%) were male, the mean patient age was 66 ± 11 years, 75 (93%) underwent ablation for AF, and the mean duration of arrhythmia was 40 ± 70 months. A total of 26 (32%) patients had a history of catheter ablation, and 2 (3%) had undergone a right-sided surgical maze procedure. Six (7%) patients were diagnosed previously with sick sinus syndrome. All e-SAN mappings were performed before SVC isolation, without or after transient isoproterenol infusion, and the mean heart rate (HR) during mapping was 67 ± 16 beats per minute (bpm).

e-SAN location from the CT top and the RSPV roof

Measurement results of each distance and proportion are shown in Table 2 and Figure 2. The relative height of the e-SAN from the CT top was −3.5 ± 10.3 mm (range, −37.0–

13.0 mm). Meanwhile, the relative height of the e-SAN from the RSPV roof was −19.8 ± 12.8 (range, −50.0–4.0) mm, which was significantly higher than that from the CT top ($p < 0.001$). Furthermore, the mean distance from the CT top and the RSPV roof to the electrical SAN was 7.9 ± 7.5 and 20.0 ± 12.4 mm, respectively, and e-SAN was distributed closer to the CT top. The e-SAN was located at the level of or below the CT top in 54 (67%) patients, and in 77 (95%) patients, the e-SAN was located at the same level as or under the RSPV roof (Figure 2).

Results of the logistic regression analysis of the baseline parameters for predicting a higher e-SAN location than the CT top case are shown in Table 3. In the univariate analysis, a faster HR during e-SAN mapping and larger left atrial dimensions were significant predictors for identifying those in whom the location of the e-SAN was higher than the CT top and remained significant after adjusting for age and sex (HR: adjusted OR per 10 increase: OR 1.60, 95% CI 1.15–2.22, $p < 0.01$; left atrial dimension: adjusted OR 0.92, 95% CI 0.85–0.99, $p < 0.05$). No significant relationship was found with age, sex, hypertension, congestive heart failure, sick sinus syndrome, or prior cardiac surgery.

New anatomically based SVC isolation reference and SVC sleeve lengths: 10 mm above the CT top vs. the RSPV roof

As the RSPV roof was located above the e-SAN in 95% of the patients in this study, we set 10 mm above the CT top as the new anatomically guided SVC isolation reference, which was located higher than the e-SAN in 78 (96%) patients (Figure 2).

The SVC sleeve lengths from 10 mm above the CT top were significantly longer than those from the RSPV roof (28.7 ± 11.2 vs. 22.5 ± 11.3 mm, $p < 0.001$).

[insert Figure2]

SVC isolation and ablation height

In this study, 18 patients underwent SVC isolation during the ablation procedure. Bidirectional block between the SVC and RA was achieved in all patients with 19 ± 7 radiofrequency applications, and no patient had sinus node dysfunction, required pacemaker implantation, or had phrenic nerve injury. The height of the ablation line from the e-SAN was 17.7 ± 10.0 mm, which was 11.1 ± 3.4 mm from the CT top and −5.8 ± 10.2 mm from the RSPV roof.

Discussion

The main findings of this study are as follows: (1) ICE-guided anatomically defined

SAN (CT top) could be used to predict the height of the e-SAN; (2) SVC isolation 10 mm above the CT top can ensure longer sleeve and is as secure as using the RSPV roof as a landmark in terms of avoiding e-SAN injury during SVC isolation; and (3) SVC isolation using the CT top as a landmark provides additional information that could guide the physician in locating the boundaries of the e-SAN.

Elimination of arrhythmogenic triggers is the standard strategy of catheter ablation for AF, and PV isolation is the most common procedure because triggers of AF usually originate from the PVs[11]. However, SVC isolation is another procedure to control AF, as the myocardial sleeves of the SVC serve as non-PV foci site in 6-12% of AF patients, and long SVC could be a substrate for the maintenance of AF[1, 2, 12]. Determining the e-SAN is important before performing SVC isolation, as sinus node dysfunction is a well-known complication of this procedure[13-15]. In general, SVC isolation is performed at or above the SVC-RA junction, and several methods can be employed to identify this landmark. The electrically defined SVC-RA junction is the site where both atrial and SVC potentials are recorded on the same electrode[16, 17]. However, these electric-based methods require restoration of sinus rhythm, which in some cases cannot be achieved due to rapid initiation of AF before the sinus beat is restored after electrical cardioversion.

Our study proposed a novel ICE-based method which uses the CT top, which is an established histological location, as a reference point to identify the e-SAN. Most (96%) of the e-SAN were located 10 mm above or below the point of the CT top, distributed widely toward the inferior vena cava, which was consistent with the histological position of the SAN cell along the crista terminalis. In previous studies, the anatomically defined landmarks for the SVC-RA junction were reported as the point where the cylindrical SVC dilates into the RA as visualized by angiography or geometry created by three-dimensional anatomical mapping systems or the lower RPA border with ICE projection from inside the SVC[2-4, 16]. According to our results, the former reference is not sufficient to prevent sinus node injury, as these points are at least equal to or lower than the CT top, because the highest point of the CT corresponds to the upper point of the deflection. Conversely, the RSPV roof, which was a substitute of the later reference points in this study, was a good marker for identifying the ablation height in terms of avoiding e-SAN injury, because 95% of the e-SAN were located below this level. In patients who had undergone SVC isolation without e-SAN dysfunction in the study population, the actual ablation height was lower than the RSPV roof and 11 mm higher than the CT top. Based on these results, whenever it is difficult to restore sinus rhythm in order to identify the e-SAN, maintaining a certain distance above the CT top

during radiofrequency energy application, specifically 10 mm above the expected ablation radius, is required regardless of the location of the e-SAN, to avoid e-SAN injury.

Further, when we compare the SVC isolation references from another viewpoint, at the level of 10 mm above the CT top, it is possible to isolate a longer lesion of the SVC than at the RSPV roof, and this may be more effective in controlling arrhythmias by blocking additional triggers, and the substrate of AF as extensive encircling PV isolation has been reported to be better than ostial isolation[18].

In addition to providing a new reference point for SVC isolation, our results reveal that a higher HR correlated with a higher e-SAN location to a greater extent than the CT top. Therefore, caution should be taken during SVC isolation, and the highest level of the e-SAN should be used.

Histological examination reveals that the SAN cell complex is structurally and electrically isolated by fat and connective tissue with few extensions into the surrounding atrial myocardium[6]. Optical mapping using isolated human hearts revealed that multiple exits form specialized sinoatrial electrical conduction pathways[19]. Moreover, the major exits to the RA shift in response to autonomic influences, and correlation with the HR was observed in both animal and human models[20-22]. These

characteristics might be attributed to a higher e-SAN location in those with a higher HR. That is, the e-SAN acquired during lower HR does not always represent the highest electrical exit from the SAN complex, and those patients could have a higher risk of SAN complex injury during SVC isolation if we only refer to the e-SAN. Although there are a limited number of patients who require permanent pacemaker implantation due to SAN dysfunction caused by SVC isolation, recent reports indicate that there is a latent SAN dysfunction characterized only by reduction in the maximum HR during exercise after SVC isolation[23]. This implies that there are cases where potential complications of the SAN injury are overlooked. Given that the highest exit would not be far from the expected histological upper position, the ICE-guided anatomically defined SAN would provide useful SAN complex positioning information for patients in whom sinus rhythm is restored.

Limitations

The results of our study were limited by the single-center, retrospective design of the study and the relatively small sample size. In echo studies, identification of the SVC and RA connection varies between physicians due to differences in the interpretations of ICE images, which may explain the few cases that showed a very high e-SAN compared

with the CT top. The utility of the current CT top-based SVC isolation reference should be investigated in future studies.

Conclusions

The highest point of the CT determined by the ICE-guided approach is a useful anatomical landmark in predicting the upper limit of the e-SAN. This provides useful information about the SVC isolation height especially when e-SAN cannot be mapped due to failure of maintaining sinus rhythm.

Acknowledgments

We would like to thank Keisuke Date, Nana Sukeda, Tomoyu Kondo, Hironori Nakazaki, and Koji Ogawa for their valuable assistance in obtaining electroanatomical mapping data, and Editage (www.editage.com) for English language editing.

Reference List

1. Tsai CF, Tai CT, Hsieh MH, Lin WS, Yu WC, Ueng KC, Ding YA, Chang MS, Chen SA. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava: electrophysiological characteristics and results of radiofrequency ablation. Circulation 2000;102:67-74.

2. Arruda M, Mlcochova H, Prasad SK, Kilicaslan F, Saliba W, Patel D, Fahmy T, Morales LS, Schweikert R, Martin D, Burkhardt D, Cummings J, Bhargava M, Dresing T, Wazni O, Kanj M, Natale A. Electrical isolation of the superior vena cava: an adjunctive strategy to pulmonary vein antrum isolation improving the outcome of AF ablation. J Cardiovasc Electrophysiol 2007;18:1261-1266.

3. Chang HY, Lo LW, Lin YJ, Chang SL, Hu YF, Feng AN, Yin WH, Li CH, Chao TF, Hartono B, Chung FP, Cheng CC, Lin WS, Tsao HM, Chen SA. Long-term outcome of catheter ablation in patients with atrial fibrillation originating from the superior vena cava. J Cardiovasc Electrophysiol 2012;23:955-961.

4. Chen G, Dong JZ, Liu XP, Zhang XY, Long DY, Sang CH, Ning M, Tang RB, Jiang CX, Ma CS. Sinus node injury as a result of superior vena cava isolation during catheter ablation for atrial fibrillation and atrial flutter. Pacing clin electrophysiol 2011;34:163-170.

5. Steven D, Roberts-Thomson KC, Seiler J, Michaud GF, John RM, Stevenson

WG. Fibrillation in the Superior Vena Cava Mimicking Atrial Tachycardia. Circ Arrhythm Electrophysiol. 2009;2:e4-e7**6.** Sánchez-Quintana D, Cabrera JA, Farré J, Climent V, Anderson RH, Ho SY. Sinus node revisited in the era of electroanatomical mapping and catheter ablation. Heart 2005;91:189-194.

7. Matsuyama TA, Inoue S, Kobayashi Y, Sakai T, Saito T, Katagiri T, Ota H. Anatomical diversity and age-related histological changes in the human right atrial posterolateral wall. EP Europace 2004;6:307-315.

8. Marrouche NF, Martin DO, Wazni O, Gillinov AM, Klein A, Bhargava M, Saad E, Bash D, Yamada H, Jaber W, Schweikert R, Tchou P, Abdul-Karim A, Saliba W, Natale A. Phased-array intracardiac echocardiography monitoring during pulmonary vein isolation in patients with atrial fibrillation: impact on outcome and complications. Circulation 2003;107:2710-2716.

9. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-458.

10. Fisher CM. Lacunes: Small, deep cerebral infarcts. Neurology 1965;15:774-774.

11. 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 1998;339:659-666.

12. Higuchi K, Yamauchi Y, Hirao K, Sasaki T, Hachiya H, Sekiguchi Y, Nitta J, Isobe M. Superior vena cava as initiator of atrial fibrillation: Factors related to its arrhythmogenicity. Heart Rhythm 2010;7:1186-1191.

13. Fenelon G, Franco M, Arfelli E, Okada M, De Araujo S De Paola AA. Acute and chronic effects of extensive radiofrequency lesions in the canine caval veins: implications for ablation of atrial arrhythmias. Pacing clin electrophysiol 2006;29:1387-1394.

14. Sacher F, Monahan KH, Thomas SP, Davidson N, Adragao P, Sanders P, Hocini M, Takahashi Y, Rotter M, Rostock T, Hsu L-F, Clémenty J, Haïssaguerre M, Ross DL, Packer DL, Jaïs P. Phrenic Nerve Injury After Atrial Fibrillation Catheter Ablation: Characterization and Outcome in a Multicenter Study. J Am Coll Cardiol 2006;47:2498-2503.

15. Higuchi K, Yamauchi Y, Hirao K. Superior Vena Cava Isolation In Ablation Of Atrial Fibrillation. J Atr Fibrillation 2014;7:1032-1032.

16. Higa S, Tai CT, Chen SA. Catheter ablation of atrial fibrillation originating from extrapulmonary vein areas: Taipei approach. Heart Rhythm 2006;3:1386-1390.

17. Nakamura T, Hachiya H, Yagishita A, Tanaka Y, Higuchi K, Kawabata M, Sasano T, Hirao K. The Relationship between the Profiles of SVC and Sustainability of SVC Fibrillation Induced by Provocative Electrical

Stimulation. Pacing Clin Electrophysiol 2016;39:352-360.

18. Proietti R, Santangeli P, Di Biase L, Joza J, Bernier ML, Wang Y, Sagone A, Viecca M, Essebag V, Natale A. Comparative Effectiveness of Wide Antral Versus Ostial Pulmonary Vein Isolation. Circ Arrhythm Electrophysiol 2014;7:39-45.

19. Fedorov VV, Glukhov AV, Chang R, Kostecki G, Aferol H, Hucker WJ, Wuskell JP, Loew LM, Schuessler RB, Moazami N, Efimov IR. Optical mapping of the isolated coronary-perfused human sinus node. J Am Col Cardiol 2010;56:1386-1394.

20. Boineau JP, Schuessler RB, Hackel DB, Miller CB, Brockus CW, Wylds AC. Widespread distribution and rate differentiation of the atrial pacemaker complex. Am Journal Physiol 1980;239:406-415.

21. Kalman JM, Lee RJ, Fisher WG, Chin MC, Ursell P, Stillson CA, Lesh MD, Scheinman MM. Radiofrequency catheter modification of sinus pacemaker function guided by intracardiac echocardiography. Circulation 1995;92:3070-3081.

22. 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;77:1221-1237.

23. Hayashi T, Mizukami A, Kuroda S, Matsumura A, Goya M, Sasano T. Sinus node dysfunction characterized by reduction only in maximum heart rate during exercise after superior vena cava isolation in atrial fibrillation catheter ablation; A potential complication. HeartRhythm Case Reports 2020;6:206-209.

Figure legends

Figure 1. Definition of each reference and measurement method

A. The earliest right atrial activation site during sinus rhythm was depicted as the electrical sinoatrial node (e-SAN) (red star). The highest point of the crista terminalis (CT), which was visualized as the upper edge of the right atrial appendage by two-dimensional intracardiac echocardiography, was depicted as the CT top (blue circle).

B. The superior vena cave (SVC) isolation reference was set 10 mm above the CT top (gray line). The intersection of the right superior pulmonary vein (RSPV) and the middle line of the SVC in the anteroposterior view was depicted as the RSPV roof (pale blue circle), which is the conventional SVC isolation reference height.

C. In the fast anatomical map of the right atrium, SVC, left atrium, and pulmonary veins, the e-SAN (right-sided white tag), the CT top (left-sided white tag) point, and grid scale, with the grid size of the squares configured to 10 mm, are also displayed on the same screen in the anteroposterior view using CARTO3. Tags are depicted as a red star, blue and pale blue circles in the enlarged view. The relative height of the e-SAN from the CT top and RSPV roof on the craniocaudal axis was measured.

RAA, right atrial appendage; RPA, right pulmonary artery

Figure 2. Height of each anatomical reference

Box plot and 90th percentile standard error of the electrical sinoatrial node (e-SAN) height from the highest point of the crista terminalis (CT top) (left) and the roof of the right superior pulmonary vein (RSPV roof) (right). The median height of the e-SAN in each plot was placed at the same level (red line). Ninety-six percent of the e-SAN were located 10 mm above or below the CT top (gray line), which is proposed as the anatomical reference of superior vena cava isolation in this study, and those with 95% are located at the level of or below the RSPV roof (right plot). Schemes of the relationship between the e-SAN (red star), the CT top (blue circle), and the RSPV roof (pale blue circle) locations are shown in each box.