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Respiratory Cycle-Dependent Atrial Trachycardia; its Unique Characteristics and Relation with Autonomic Nerve System

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Abstract

Respiration influences the sinus heart rate, however, little is still known about the tachyarrhythmias related to respiration. Atrial tachycardia (AT) rarely emerges during inspiration and it also ceases during expiration. This type of AT is thus called respiratory cycle-dependent atrial tachycardia (RCAT), and it demonstrates a centrifugal activation pattern. Based on these peculiar P wave morphologies, the foci converged either around the right superior pulmonary vein (RSPV) or inside the superior vena cava where the anterior right ganglionated plexi (ARGP) is considered to be located. The mechanism of such AT is therefore thought to be related to the activity of the autonomic system.

Introduction

The variability of the sinus heart rate by respiratory cycles has been well recognized in the relationship between respiration and normal heart beat, in which R-R intervals are shortened during inspiration and prolonged during expiration.[1] The possible mechanisms for this variability include pulmonary reflexes,[1] baroreflex,[2] diastolic filling of the heart during inspiration,[3] and a central nervous system mechanism.[4] Because these mechanisms mainly work via the autonomic nervous system, it is thought that the autonomic nervous system plays a major role in the interaction between respiration and sinus rhythm.

On the other hand, an interaction between respiration and supraventricular arrhythmias is also seen in rare cases. Respiratory cycle-dependent atrial tachycardia (RCAT), which is a focal atrial tachycardia (AT) that repeatedly appears and disappears in synchrony with respiratory cycles, was first reported by Takatsuki et al.[5] This case report described that bursts of focal AT with an origin in the left atrial posterior wall repeatedly appeared during inspiration and ceased during expiration. Another report[6] in 2001 described a similar case with atrial fibrillation (AF), which showed the onset of AF at inspiration and resumed sinus rhythm at expiration in a repeated manner, and in which temporal vagal activation or pulmonary vein (PV) stretch by an increased venous return was assumed as the cause of the arrhythmia. Furthermore, a recent report[7] showed that the origin of RCAT converged on the narrow area, and that this convergence clarified the etiology and the mechanism of RCAT. The autonomic nervous system of the heart and the actual mechanism of supraventricular arrhythmia onset have attracted attention. Catheter ablation targeting ganglionated plexi (GP), which are autonomic ganglia on the surface of heart, has been performed in recent years to treat AF. The main mechanism of on set and abeyance of RCAT may be GP mediated au-

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tonomic modulation during the respiration cycle.

We now review these available literature regarding RCAT, discuss outcomes related to catheter ablation, and discuss hypothetical mechanisms behind the genesis of these arrhythmias and how these may impact their response to catheter ablation and/or pharmacologic management.

Prevalence and Clinical Characteristics

RCAT reportedly accounts for 13% of focal AT.[7] This high prevalence population means that no distinctive risk factors were identified in this population, but RCAT was often missed. As a result, we may recognize more respiratory cycle-dependent arrhythmia cases, if the patients with atrial premature beats are included. The clinical characteristics of the nine reported patients and 11 RCATs[5-7] are presented in Table 1. Sex ratio, age, characteristics of underlying heart disease does not differ significantly between patients with RCAT and those with any other types of focal AT.[7] No detectable structural heart disease was observed in any of the patients except for one in whom an uncontrollable RCAT and concomitant paroxysmal AF provoked tachycardia induced cardiomyopathy with a depressed left ventricular ejection fraction. All RCATs were recognized before the EP study with simultaneous recordings from the ECG and respiratory monitor (Figure 1). The morphology of the P wave in the body surface ECG during the tachycardia was almost analogous in the latest report, [7] which exhibited a positive deflection in leads I, II, aVF, and V2-6. The P wave morphology in V1 was positive in six RCATs and biphasic (positive to negative) in the other three RCATs (Table 2). The RCAT emerged during exercise in two patients, during sleep in one patient who was complicated with untreated severe sleep apnea syndrome with an apnea-hypopnea index of 43,and in no particular condition in the other patients. RCAT is particularly characterized by its origin localized to the right superior pulmonary vein, superior vena cava, or the surrounding area. This characteristic is important for discussing the mechanism of RCAT.

Pharmacological Properties

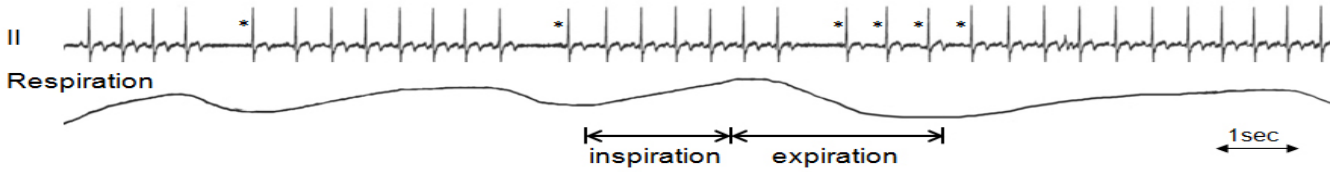
RCATs are refractory to 2.7 ± 0.7 drugs including class I antiarrhythmic agents and beta blockers.[7] And some adrenergic or antiadrenergic agents, such as isoproterenol and landiolol, affect the mean AT cycle length and the RCAT inducibility. In contrast, 0.25 mg of atropine, parasympathetic antagonist, has no effect on the RCAT. These facts reveal a relationship between autonomic nerve activity and the etiology and the mechanism of RCAT. The occurrence of RCAT is reproducibly suppressed by bolus infusion of low dose (5mg) adenosine triphosphate.These characteristics

Table 1 Clinical Characteristics in the Patients with RCAT and RCAF

Study	Number of Patients	Age	Sex	Origin of AT or AF	Ablation Site	Ablation Site
Takatsuki, et al[5]	1	51	M	focal AT	LA posterior wall	AT focus
Lin, et al[6]	1	67	M	AF	no described	-
Yamamoto, et al[7]	7	54	M	focal AT	RSPV and SVC	PV and SVC isolation
		54	F	focal AT	RSPV antrum	AT focus
		58	f	focal AT	RSPV and SVC	PV and SVC isolation
		72	M	focal AT	RSPV antrum	AT focus
		38	M	focal AT	SVC	AT focus
		70	M	focal AT	RSPV antrum	AT focus

RCAT: respiratory cycle-dependent atrial tachycardia, RCAF: respiratory cycle-dependent atrial fibrillation, AT: atrial tachycardia, LA: left atrium, AF: atrial fibrillation, RSPV: right superior pulmonary vein, SVC: superior vena cava

Figure 1: Simultaneous Recordings of the Body Surface Electrocardiogram and Respiration Monitor. Respiratory Cycle-Dependent Atrial Tachycardia was Characterized by Atrial Ectopic Bursts which Emerged After Starting Inspiration and then Ceased During Expiration. The Asterisks in the Electrocardiograms Indicate Sinus Beats



are also important in discussing the mechanism.

Strategy, Efficacy, and Long-Term Outcome of Catheter Ablation

Radiofrequency energy application in the thoracic veins including the right superior pulmonary vein (RSPV) and superior vena cava (SVC) has been avoided in the ablation procedure for patients with AF, to prevent venous injury or stenosis, and antrum ablation for electrical isolation has often been performed. On the other hand, focal energy deliveries in the thoracic veins have been reported to be safe and associated with a good long-term success in the RFCA procedure for focal ATs.[8] Both the thoracic vein isolation strategy and focal ablation strategy in the RFCA are performed for RCATs originating from inside the thoracic veins (Table 1); but focal radiofrequency energy application can be used in patients exhibiting such RCATs. Table 1 shows that acute success in the first ablation procedure was achieved in all eight patients. The electroanatomical map of all RCATs exhibited a centrifugal activation pattern. The sites of earliest activation were seen at the antrum of the RSPV, inside the RSPV, and inside the SVC. Two patients had two distinct RCATs arising from inside the RSPV and inside the SVC. Electrical isolation of the RSPV and SVC was performed in these two patients, which resulted in the complete suppression of all RCATs with no ectopic beats inside these vessels. A focal radio frequency energy delivery at the earliest activation site successfully eliminated the RCATs in the other six patients. One patient underwent further isolation of the other three PVs due to concomitant paroxysmal AF frequently provoked by short coupled ectopic beats originating from inside the left superior PV. All patients were followed without any antiarrhythmic agents or beta-blockers. No AT was observed in any of the patients during the follow-up period, except for one in whom an RCAT recurred two days after the first procedure. A second procedure was performed in this patient three days after the recurrence, which successfully eliminated the tachycardia. There were no significant differences in the acute success rate and long-term outcomes after RFCA between the patients with RCAT and those with other types of focal AT.

Mechanism

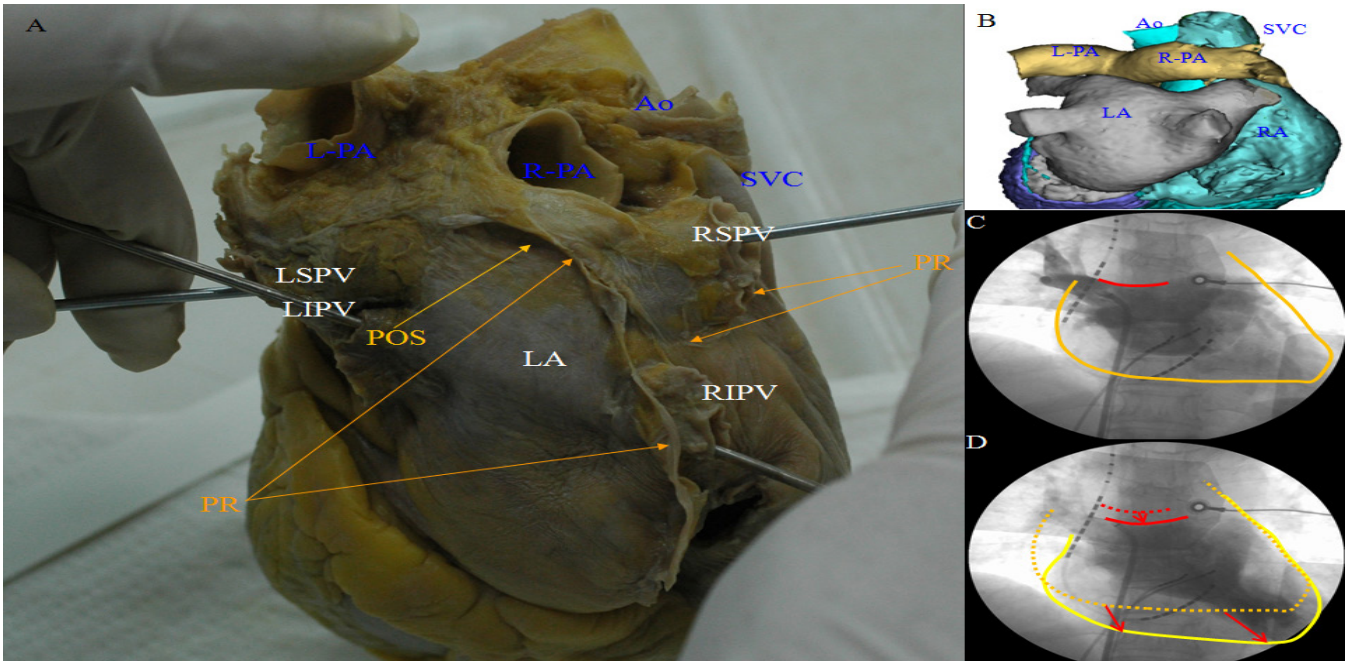
Table 3 shows the summary of possible mecha-

Table 2 Clinical Characteristics in the Patients with RCAT and RCAF

Patient	I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6
1	+	+	+	-	-	+	+	+	+	+	+	+
	+	+	+	-	flat	+	+/-	+	+	+	+	+
2	+	+	+	-	-	+	+	+	+	+	+	+
3	+	+	+	-	-	+	+	+	+	+	+	+
	+	+	+	-	-	+	+/-	+	+	+	+	+
4	+	+	-/+	-	+	+	+	+	+	+	+	+
5	+	+	-	-	+	+	+	+	+	+	+	+
6	+	+	+	-	-	+	+/-	+	+	+	+	+
7	+	+	+	-	+	+	+	+	+	+	+	+

RCAT: RCAT: respiratory cycle-dependent atrial tachycardia, +: positive deflection, -: negative deflection, +/-: positive to negative biphasic deflection,-/+: negative to positive biphasic deflection

Figure 2: Posterior View of the Dissected heart. **B:** The Same View of the 3-Dimensional Cardiac Computed Tomography. The Figure of Dissected Heart Shows the Positional Relationship of the Right Superior Pulmonary Vein (RSPV), Superior Vena Cava (SVC), and Pericardial Reflection (PR). The Reflection of the Pericardium at the Postcaval Recess, Right Pulmonary Venous Recess, and Pericardial Oblique Sinus (POS) Anchors the Heart to the Mediastinum. **C:** The Contrast Radiography of the Left atrium at Deep Expiration **D:** The Same at Deep Inspiration. The Movement Length of Lower Side in this Figure During the Respiratory Cycle is Longer than the Upper Side where is Anchored to the Mediastinum. For Details, See Text



nism in RCAT.

The origins of RCAT are concentrated at the area (around SVC and RSPV) of the anterior right GP (ARGP). There is prolonged sinus rhythm cycle during the current application to RCAT, suggesting that GP is near the application site.[9] ARGP is a ganglion containing both sympathetic and parasympathetic nerve components. [10] Each GP is known to be near the PV efferent nerve axons are distributed from nerve cells of the GP to the atrial wall, and that the change in autonomic activity via the GP directly shallows the resting membrane potential of the atrial muscle and causes a change in arrhythmogenicity.[11-14] Interestingly, ARGP is considered to be particularly important for the onset of AF in those with sleep apnea syndrome.[12] The interaction between respiration and autonomic nerves has been carefully examined in terms of the change in sinus rhythm cycle by respiration. Although the precise mechanism of the change in sinus cycle length by respiration has not been fully elucidated, it was considered to result mainly from the suppression of parasympathetic nerve activity at inspiration.[1-4] These respiratory cycle-dependent changes in parasympathetic nerve activity, however, are unlikely to be a mechanism of RCAT because previous studies demonstrated that stimulating, not suppressing, parasympathetic nerve activity causes firing in the pulmonary vein.[15] The intravenous atropine injection does not suppress RCAT, which further bolsters this theory.[7] The quickness of the change in sympathetic nerve activity is thought to be too slow to keep up with the respiratory cycle. However, the change in sympathetic nerve activity can synchronize with the respiratory cycle: the activity is stimulated after the start of inspiration and reaches a peak at the deepest inspiration.[16] The efferent components of sympathetic nerve activity are mainly regulated by the interaction between the respiratory center in the brain stem and the sympathetic nerve system.[17, 18]A sympathomimetic drug is required to induce RCAT in some cases, and exercise load also induces RCATs. Therefore, changes in the sympathetic nerve activity may be a predominant mechanism of RCAT. Other possible etiologies of RCAT include the physical stimulus by extension of the atrium and thoracic veins. Previous studies demonstrated that acute stretch increases the effective refractory period of the atrial tissue, which could induce triggered activity.[17, 18] There are two possible mechanisms for the atrial stretch during the

Table 3 Summary of Possible Mechanism of RCAT

a. Mechanism of Dependence on Respiratory Cycle			
autonomic nerve system		physical stimulus by strech of the venous or atrial wall	
GP localization sympathetic nerve activity change		movement of the heart	increase of venous return
b. Mechanism of RCAT Firing			
supportive phenomena	triggered activity	automacity	
	existing preceding action potentials ceased by adenosine triphosphate infusion no warm up and no cool down phenomena	None	

RCAT: respiratory cycle-dependent atrial tachycardia, GP: ganglionated plexi

respiration cycle. First, the movement of the heart inside the mediastinum with respiration may result in the acute tissue stretch. The RCAT foci are located in the area where the heart is anchored to the mediastinum by the pericardial reflection at the postcaval recess, right pulmonary venous recess, and oblique sinus. [7, 19] Figure 2 shows the dissection of the heart, demonstrating a positional relationship of the RSPV, SVC, and pericardial reflection. Respiratory movement during inspiration can result in local atrial or venous wall stretch. Second, stretch of the venous or atrial wall could be considered as another possible etiology of atrial muscle stimulus, since there is inspiratory augmentation of the venous return to the right sided heart system. An experimental study by Olsen, et al.,[20] however, reported that the left ventricular end-diastolic volume remains essentially constant during the respiratory cycle, and a clinical study[21] measuring the intra-cavity pressure during left atrial catheterization showed no increase in the left atrial pressure during inspiration.

Several observation in previous studies[5, 7] suggest triggered activity as a part of the mechanism of the RCAT. First, electrical isolation of these vessels completely suppresses the RCATs in patients with two distinct RCATs originating from inside the RSPV and SVC, with no ectopic beats inside these vessels, thus indicating that the tachycardia requires preceding action potentials to develop. Second, the RCATs ceases after a bolus infusion of adenosine triphosphate. These are findings characteristic of triggered activity.[22] Further, exercise and the administration of a beta-adrenergic agonist, which induces the RCATs, are also suggestive of triggered activity.[22]

Clinical approach

Clinical approach methods regarding the diagnosis, follow-up, treatment protocol, etc. of RCAT are fundamentally the same as for other types of AT. In this regard, catheter ablation is considered to be the safest and most certain method. This is because it is drug resistant in the reported cases described above.[7] It has also been clarified that the cycle length of RCAT extends due to the administration of beta blocker during electrophysiological studies, so heart rate control of RCAT may be possible. However, in our experience, even if the heart rate may be controlled, it is difficult to sufficiently suppress the symptoms of the patient and to improve their quality of life.

Conclusions

RCAT accounts for 13% of all types of focal AT, and is typically characterized by an origin localized to SVC, RSPV, or the surrounding area. Triggered activity is suggested to be the mechanism of the tachycardia. Possible etiology of the respiratory cycle-dependent appearance and disappearance of RCAT include cyclic changes of sympathetic nerve activity and physical stimulus to the left atrium or thoracic veins by tissue extension.

Disclosures

No disclosures relevant to this article were made by the authors.

References

1. Melcher A. Respiratory sinus arrhythmia in man. A study in heart rate regulating mechanisms. Acta Physiol Scand Suppl. 1976;435:1-31
2. Okada H. Reflex responses to stimulation of baroreceptors in the right subclavian artery. Am J Physiol. 1964;206:918-922
3. Bainbridge FA. The influence of venous filling upon the rate of the heart. J Physiol. 1915;50:65-84
4. Levy MN, DeGeest H, Zieske H. Effects of respiratory center activity on the heart. Circ Res. 1966;18:67-78
5. Takatsuki S, Mitamura H, Miyoshi S, Ogawa S. Respiratory cycle-dependent left atrial tachycardia. J Cardiovasc Electrophysiol. 2001;12:1202
6. Lin PH, Huang JL, Ting CT, Chen SA. Respiration and initiation of atrial fibrillation. J Cardiovasc Electrophysiol. 2001;12:979
7. Yamamoto T, Hayashi M, Miyauchi Y, Murata H, Horie T, Igawa O, Kato T, Mizuno K. Respiratory cycle-dependent atrial tachycardia: Prevalence, electrocardiographic and electrophysiologic characteristics, and outcome after catheter ablation. Heart Rhythm. 2011;8:1615-1621
8. Kistler PM, Sanders P, Fynn SP, Stevenson IH, Hussin A, Vohra JK, Sparks PB, Kalman JM. Electrophysiological and electrocardiographic characteristics of focal atrial tachycardia originating from the pulmonary veins: Acute and long-term outcomes of radiofrequency ablation. Circulation. 2003;108:1968-1975
9. Yuan BX, Ardell JL, Hopkins DA, Losier AM, Armour JA. Gross and microscopic anatomy of the canine intrinsic cardiac nervous system. Anat Rec. 1994;239:75-87
10. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, Mazzone P, Tortoriello V, Landoni G, Zangrillo A, Lang C, Tomita T, Mesas C, Mastella E, Alfieri O. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. Circulation. 2004;109:327-334
11. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec. 1997;247:289-298
12. Ghias M, Scherlag BJ, Lu Z, Niu G, Moers A, Jackman WM, Lazzara R, Po SS. The role of ganglionated plexi in apnea-related atrial fibrillation. Journal of the American College of Cardiology. 2009;54:2075-2083
13. Schauerte P, Scherlag BJ, Patterson E, Scherlag MA, Matsudaria K, Nakagawa H, Lazzara R, Jackman WM. Focal atrial fibrillation: Experimental evidence for a pathophysiologic role of the autonomic nervous system. J Cardiovasc Electrophysiol. 2001;12:592-599
14. Lim PB, Malcolme-Lawes LC, Stuber T, Weight I, Francis DP, Davies DW, Peters N, Kanagaratnam P. Intrinsic cardiac autonomic stimulation induces pulmonary vein ectopy and triggers atrial fibrillation in humans. J Cardiovasc Electrophysiol. 2011;(in press)
15. Patterson E, Po SS, Scherlag BJ, Lazzara R. Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm. 2005;2:624-631
16. Malpas SC. The rhythmicity of sympathetic nerve activity. Prog Neurobiol. 1998;56:65-96
17. Chen YJ, Chen SA, Tai CT, Wen ZC, Feng AN, Ding YA, Chang MS. Role of atrial electrophysiology and autonomic nervous system in patients with supraventricular tachycardia and paroxysmal atrial fibrillation. J Am Coll Cardiol. 1998;32:732-738
18. Satoh T, Zipes DP. Unequal atrial stretch in dogs increases dispersion of refractoriness conducive to developing atrial fibrillation. J Cardiovasc Electrophysiol. 1996;7:833-842
19. Chaffanjon P, Brichon PY, Faure C, Favre JJ. Pericardial reflection around the venous aspect of the heart. Surg Radiol Anat. 1997;19:17-21
20. Olsen CO, Tyson GS, Maier GW, Davis JW, Rankin JS. Diminished stroke volume during inspiration: A reverse thoracic pump. Circulation. 1985;72:668-679
21. Franzen OW, Klemm H, Hamann F, Koschyk D, von Kodolitsch Y, Weil J, Meinertz T, Baldus S. Mechanisms underlying air aspiration in patients undergoing left atrial catheterization. Catheter Cardiovasc Interv. 2008;71:553-558
22. Josephson ME. Supraventricular tachycardias. Clinical cardiac electrophysiology. 2008:270 - 284
23. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. Circulation. 2004;110:364-367
24. Stevenson IH, Teichtahl H, Cunnington D, Ciavarella S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. Eur Heart J. 2008;29:1662-1669
25. Fung JW, Li TS, Choy DK, Yip GW, Ko FW, Sanderson JE, Hui DS. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. Chest. 2002;121:422-429
26. Roche F, Xuong AN, Court-Fortune I, Costes F, Pichot V, Duverney D, Vergnon JM, Gaspoz JM, Barthelemy JC. Relationship among the severity of sleep apnea syndrome, cardiac arrhythmias, and autonomic imbalance. Pacing Clin Electrophysiol. 2003;26:669-677
27. Tkacova R, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation. 1998;98:2269-2275
28. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman AS, Somers VK. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003;107:2589-2594