Left Atrial Tachycardia Originating from the Mitral Annulus–Aorta Junction

Mario D. Gonzalez, MD; Leonardo J. Contreras, MD; Monique R.M. Jongbloed, MD; Jaime Rivera, MD; Timothy P. Donahue, MD; Anne B. Curtis, MD; Michael S. Bailey, MD; Jamie B. Conti, MD; Glenn I. Fishman, MD, PhD; Martin J. Schalij, MD, PhD; Adriana C. Gittenberger–de Groot, MD

Background—At the mitral annulus–aorta (MA-Ao) junction, the left atrium is continuous through the subaortic curtain with the musculature of the anterior mitral leaflet. Under experimental conditions, this region can generate abnormal electrical activity. In patients with left atrial tachycardia, we investigated whether this region could be the source of this arrhythmia.

Methods and Results—In 10 (28%) of 35 consecutive patients with left atrial tachycardia, the arrhythmia originated from the MA-Ao junction. Sustained, self-limited episodes of atrial tachycardia (cycle length, 340±56 ms; duration, 125±69 seconds) were repeatedly induced. Prematurity of the extrastimulus and time to first atrial tachycardia complex were directly correlated (R=0.66; P<0.001). During tachycardia, bipolar electrograms at the earliest site preceded onset of the P wave by 44±14 ms and were of longer duration and lower amplitude than those recorded from nearby left atrial sites (52±8 versus 24±4 ms, P<0.001; and 0.53±0.08 versus 3.45±0.96 mV, respectively; P<0.001). Ablation eliminated the tachycardia with no recurrence after a mean follow-up of 24±19 months. A comparative study in mouse embryos demonstrated the presence of the developing specialized conduction system in the MA-Ao region starting at embryonic age 11.5.

Conclusions—The MA-Ao junction can be a frequent source of left atrial tachycardia. This previously unrecognized site of origin may explain why catheter ablation has been less successful in eliminating left versus right atrial tachycardias. Remnants of the developing specialized conduction system could be the underlying substrate of this arrhythmia. (Circulation. 2004;110:3187-3192.)

Key Words: mitral valve ■ catheter ablation ■ arrhythmia ■ electrophysiology ■ mapping

Previous reports have documented that left atrial tachycardias usually originate from the pulmonary veins or atrial walls and, rarely, from the mitral annulus or left atrial appendage,1–6 yet catheter ablation is less successful at eliminating tachycardias originating from the left atrium than those arising from the right atrium,1 possibly because of difficulties in mapping and incomplete information about sites of origin. Although the mitral annulus–aorta (MA-Ao) junction (Figure 1) can be the source of arrhythmias under certain experimental conditions,7–9 the present study is the first to show that this region can give rise to atrial tachycardias in humans. In this report, we describe the electrophysiological characteristics of left atrial tachycardias originating from the MA-Ao junction.

Methods

Patients

We analyzed 35 consecutive patients with structurally normal hearts referred for catheter ablation and in whom mapping of both atria identified a focal left atrial tachycardia. In 10 (28%) of these patients, the tachycardia originated from the MA-Ao junction. These individuals, all women (mean age, 42±16 years), comprised the study population. They had documented paroxysmal atrial tachycardia for a mean of 7±5 years, refractory to a mean of 3±2 antiarrhythmic drugs. Patients complained of recurrent episodes of short-lasting palpitations that occurred several times a day. Five of these patients had a previous ablation attempt of a left atrial tachycardia at another institution. Their echocardiograms were normal, as required by the selection criteria (mean left atrial diameter, 31±5 mm; mean ejection fraction, 57±3%). All patients gave written informed consent, and the University of Florida Institutional Review Board approved this study.
Electrophysiological Study

Patients discontinued antiarrhythmic medications 2 weeks before undergoing electrophysiological study. The procedure was performed with patients in the fasting state under light sedation with intravenous fentanyl and midazolam. Multipolar electrode catheters were introduced percutaneously and positioned into the right atrial appendage, right ventricle, His bundle region, and coronary sinus. To record His bundle activation, a 7F deflectable catheter with 4 closely spaced pairs of electrodes was used. A deflectable catheter with 8 pairs of electrodes (5 mm between pairs) was advanced into the coronary sinus, with the most proximal pair of electrodes positioned at the coronary sinus ostium. Bipolar electrograms (30 to 500 Hz) and unipolar electrograms (0.5 to 500 Hz) were displayed and stored using a digital recording system (Bard Electrophysiology). Stimulation was performed at 2 to 3 times diastolic threshold, using pulses of 2-ms duration. Initially, single extrastimuli were introduced at several basic cycle lengths (400 to 600 ms). The coupling interval was decreased in 10-ms steps until atrial refractoriness was reached. If tachycardia could not be induced, rapid stimulation was used (250 to 500 ms). When required, intravenous isoproterenol (1 to 4 μg/min) were given and atrial stimulation was repeated by using extrastimuli first followed by rapid stimulation.

The diagnosis of atrial tachycardia was confirmed using these criteria: (1) atrial activation sequence during tachycardia different from that recorded during sinus rhythm; (2) atrial activation sequence during tachycardia different from that obtained during ventricular stimulation with retrograde ventriculo-atrial conduction; (3) A-A-V response after discontinuation of ventricular pacing; (4) ventricular stimulation with retrograde ventriculo-atrial conduction; (5) transient atrioventricular (AV) block during induction of tachycardia independent of a critical prolongation of the A-H interval; (6) inability to obtain concealed entrainment of the tachycardia using ventricular extrastimuli.

A left atrial origin of the tachycardia was suspected when right atrial activation was earliest in the fossa ovalis, Bachmann bundle region, triangle of Koch, or coronary sinus. The morphology of the P wave was analyzed during transient AV block or after ventricular premature beats that did not alter the atrial tachycardia. The A-H interval during tachycardia was compared with that obtained during stable right atrial stimulation at identical cycle length. Access to the left atrium for mapping and ablation was obtained through the transseptal approach, using the electrode catheters as anatomic landmarks. A 7F quadripolar ablation catheter with a 4-mm tip electrode was introduced through a preformed 8F sheath (SL1, Daig) and advanced into the left atrium. The earliest bipolar electrogram associated with a negative unipolar deflection was considered the site of atrial tachycardia origin. Electroanatomical mapping was obtained with the Carto system (n=4) or with NavX (n=1). In 5 patients, an echocardiogram (transthoracic, 3; intracardiac, 2) was used to confirm the location of the mapping catheter in relation to the MA-Ao junction.

Radiofrequency Ablation

The earliest activation site was targeted for ablation. Radiofrequency energy (10 to 50 W; maximal temperature, 60°C) was delivered between the tip electrode and a skin patch electrode positioned under the left scapula using an EPT 1000 generator (EP Technologies). The power was progressively increased until a temperature of >50°C was reached or the tissue impedance changed >10 Ω. Atrial stimulation was repeated before, during, and after isoproterenol administration for 60 minutes to confirm elimination of the atrial tachycardia. After the procedure, patients were monitored for 24 hours in a telemetry unit.

Comparative Study of the Developing Conduction System in Mouse Embryos

To test the possibility that remnants of the developing cardiac conduction system may persist in the MA-Ao region, we used a transgenic cardiac conduction system/lacZ murine strain capable of delineating the developing and mature cardiac conduction system. Twenty-three embryos of embryonic age (E) 9.5 to 15.5 days were stained for β-galactosidase activity, which produces a blue staining at the site of expression. Embryos were fixed at room temperature in 5% buffered saline. They were sliced transversely and examined using light microscopy, with attention specifically focused on the region between the aorta and the atrioventricular junction.

Data Analysis

Data are reported as mean±SD. Values were analyzed by means of the paired and unpaired Student t test. The correlation between extrastimuli coupling intervals and the interval between the extra-stimulus and the first tachycardia complex was analyzed by means of Pearson correlation analysis. The χ2 test was used to compare inducibility by single extrastimuli versus rapid stimulation. A probability value of <0.05 was accepted as statistically significant.

Results

Characteristics of Atrial Tachycardia

In 9 patients, both extrastimuli and rapid stimulation initiated atrial tachycardia; in 1 patient, only rapid stimulation induced it. Isoproterenol administration was required in 7 patients to induce tachycardia, including 2 patients who required both isoproterenol and aminophylline. During tachycardia (cycle length of 340±56 ms), the P waves were of low voltage,
broad, and notched, negative in aVL (n=9/10) and positive in leads III and V1 (n=10). Figure 2 depicts the characteristics of the P wave during atrial tachycardia. Sustained (>30 seconds), self-limited episodes of tachycardia (n=234) were repeatedly induced in all patients. Rapid stimulation was more successful than single extrastimuli in inducing atrial tachycardia (139 versus 95 episodes, \(P<0.05\)). The mean duration of atrial tachycardia was 125±69 seconds (range, 30 to 242 seconds). When all episodes initiated by atrial extrastimuli were analyzed, a direct correlation was found between prematurity of the extrastimulus and the elapsing interval to the first tachycardia complex (\(P<0.001; R=0.66\); Figure 3).

Activation at the earliest site preceded the P wave by 44±14 ms. Local bipolar and unipolar electrograms (Figure 4) at the earliest site were consistent with an area of slow conduction because local potentials were of longer duration and lower amplitude than those recorded from nearby left atrial sites (52±8 versus 24±4 ms, \(P<0.001\); and 0.53±0.08 versus 3.45±0.96 mV, \(P<0.001\); respectively). Activation at the earliest site preceded atrial activation near the His bundle by 44±13 ms, at the proximal coronary sinus (up to 2 cm from the ostium) by 46±15 ms, and at the right atrial appendage by 71±14 ms. The A-H interval during MA-Ao atrial tachycardia was shorter than that observed during right atrial stimulation at a cycle length identical to that of the tachycardia (87±34 ms versus 123±27 ms, \(P<0.05\), consistent with an atrial activation reaching the AV node through a left atrial input.\(^{10}\) Figure 5 illustrates the sequence of left atrial activation, using electroanatomic mapping during atrial tachycardia.

Atrial tachycardia terminated either spontaneously (n=126), because of premature atrial beats (n=105), or after administration of intravenous adenosine (6 mg bolus, n=3). In 7 patients, spontaneous termination always followed a gradual increase in cycle length (8±2% during the last 10±5 cycles, 97 episodes). In 3 patients, termination of the tachycardia followed alternating long-short cycles (29 episodes, Figure 6).

### Earliest Activation Site During Atrial Tachycardia

The origin of the tachycardia was confirmed through the use of biplane fluoroscopy (Figure 7). In the left anterior oblique projection, this site was situated between the 11 and 12 o’clock positions (Figures 1 and 5). In the right anterior oblique projection, the tip of the catheter was approximately 1 cm superior to the catheter recording His bundle activation. In 5 patients, an echocardiogram (transthoracic, 3; intracardiac, 2) confirmed that the catheter was in contact with the subaortic curtain or MA-Ao junction (Figure 8).

### Associated Tachycardias

A concurrent tachycardia was observed in 5 patients: slow-fast AV nodal reentrant tachycardia (n=2), fast-slow AV nodal reentrant tachycardia (n=1), and coronary sinus ostium atrial tachycardia (n=2).

### Radiofrequency Ablation

Radiofrequency ablation at the earliest atrial activation site eliminated tachycardia in all patients after a mean of 1.4±0.5 (median=1) applications of energy. Termination of atrial
tachycardia occurred after a mean of 11±9 (1 to 25) seconds of energy delivery. Atrial tachycardia terminated abruptly in 4, and after transient acceleration, in 6 patients. Mean power, temperature, and impedance were 33±8 W, 49±3°C, and 89±5 Ω, respectively. No changes in AV nodal conduction were found after successful ablation. All associated tachycardias were successfully eliminated. During a follow-up period of 24±19 months on no antiarrhythmic medications, no patients had recurrent tachycardia.

Developing a Murine Cardiac Conduction System
In the earliest stages examined, stage E 9.5 and E 10.5, septation between the aorta and the pulmonary artery had not occurred yet, so the outflow tract still consisted of a common trunk. Also, the AV canal was still a common canal that was situated mainly above the primitive left ventricle. In these early stages, CCS/lacZ was already present at the AV canal, which became continuous with a band of lacZ present at the junction with the outflow tract. At stage E 11.5, a separate aorta and pulmonary trunk could be observed and at stage E 12.5 the mitral and tricuspid orifices were situated above the left and right ventricle respectively. Starting at stage E 11.5, the developing conduction system was observed running between the aorta and the mitral annulus (Figure 9, left panel).22 We created 3-D reconstruction of an embryo of age E 12.5 to visualize the distribution of CCS-lacZ in the MA-Ao region. In this reconstruction, a bundle of fibers running in the retro-aortic position at the junction with the AV canal is clearly demonstrated (Figure 9, right panel). This region corresponds to the site of origin of the atrial tachycardia observed in our patient population. At a later stage (E 15), the staining of the conduction system was markedly reduced indicating regression of this system in older embryos.

Discussion
The present study demonstrates that the MA-Ao junction can be the source of focal atrial tachycardia in patients with structurally normal hearts. This previously unrecognized site of origin might partially explain why catheter ablation has been less successful at eliminating left versus right atrial tachycardias.1 The presence of fractionated, low-voltage electrograms at the earliest activation site is consistent with a

Figure 5. Sequence of left atrial activation using electroanatomic mapping during atrial tachycardia. Left upper insert shows a coronal section across the aorta and mitral annulus of a spiral CT obtained from the same patient. Earliest activation (arrow) site is located at the junction of the mitral annulus with the aorta and approximately 1 cm superior to the site where His bundle (HB) activation was recorded. Ao indicates aorta; MA, mitral annulus; and PV, pulmonary vein.

Figure 6. Spontaneous termination of atrial tachycardia preceded by beat-to-beat oscillations in cycle length. CS indicates coronary sinus; HB, His bundle; MAP, mapping catheter; and RAA, right atrial appendage. Values are in milliseconds.

Figure 7. Position of the tip of the mapping catheter at the site of atrial tachycardia origin as viewed from the right anterior oblique (RAO) and left anterior oblique (LAO) projections. The mapping catheter (MAP) has been advanced through a pre-formed sheath into the left atrium after transseptal puncture and positioned at the MA-Ao junction. CS indicates coronary sinus; HB, His bundle; and RAA, right atrial appendage.
region of slow conduction. On the other hand, the mode of initiation of this tachycardia suggests triggered activity as the mechanism of this arrhythmia. The presence of both abnormal conduction and abnormal automaticity in this region is consistent with previous observations in animal studies.7–9

The MA-Ao Junction and the Anterior Mitral Valve Leaflet

The MA-Ao junction is not simply formed by two opposing fibrous annuli. A common structure, the subaortic curtain,14–17 simultaneously supports 2 of the aortic cusps (left coronary and noncoronary) and the anterior leaflet of the mitral valve. In other words, at the MA-Ao junction, the left atrial wall does not join the left ventricular wall but is attached to the aorta. More important, the muscle fibers of the left atrium are continuous with those of the anterior mitral valve leaflet.7–9,18 Notably, microelectrode studies have shown that although the leaflet musculature resembles atrial muscle, the action potentials have AV nodal–type characteristics.7–9 These unique properties can be explained by calcium dependent cells, responsive to adenosine and similar to AV nodal cells.18 Similar to our findings in humans, experiments in animals have shown that cells from the mitral annulus and the anterior mitral leaflet can give rise to triggered activity under the influence of catecholamines.7–9

Characteristics of MA-Ao Atrial Tachycardia

Despite isoproterenol administration, most episodes of atrial tachycardia were self-limited, either due to spontaneous termination or after atrial premature beats. Therefore, atrial stimulation was frequently required to reinduce the tachycardia to identify the site of origin. In three patients with prolonged episodes of tachycardia, adenosine (6 mg intravenous bolus) terminated the tachycardia. This response as well as the mode of initiation suggests triggered activity. Importantly, there was a consistent relation between the coupling interval of the extrastimulus and the interval between the extrastimulus and the first beat of the tachycardia, consistent with triggered activity.19

The finding that the A-H interval was shorter during MA-Ao atrial tachycardia than during right atrial stimulation at identical cycle length is consistent with the wavefront entering the AV node using the left-sided input to the A-V node.10

Previous Studies

Matsuoka and colleagues2 described a patient with 2 closely located atrial tachycardias originating from what they called left anteroseptum. Their Figure 2, however, suggests the origin actually might have been the MA-Ao junction. Interestingly, they also described the presence of fractionated potentials in this region, an observation that mirrors our findings. Other authors have also shown that the mitral annulus can be the source of atrial tachycardias.6,20,21 The present study extends the findings made by Kistler et al6 in patients with atrial tachycardia arising from the mitral annulus. These authors found that the tachycardia originated close to.

Figure 8. Intracardiac echocardiogram displaying the tip of the catheter recording the origin of the tachycardia. The tip of the catheter (arrow) is in contact with the subaortic curtain, which represents the junction of the aortic cusps and the anterior leaflet of the mitral valve. Ao indicates aorta; MV, mitral valve; and PA, pulmonary artery.

Figure 9. Observations in the CCS-lacZ transgenic mouse model. Left panel demonstrates a transverse section through the heart of an embryo of 12.5 days. Immunohistochemical staining was performed with a monoclonal anti-muscle actin-α antibody to produce a double staining with CCS-lacZ. Slices were counterstained with hematoxylin. CCS-lacZ is present in the retroaortic position (arrow), at the junction with the AV canal. Right panel demonstrates a 3D reconstruction obtained from serial microscopic images of the same embryo, demonstrating the same bundle of lacZ-positive tissue (arrow). Heart is depicted from a frontal and cranial view. Different cardiac compartments are color-coded: yellow, left atrium; orange, right atrium; red, left ventricle and aorta; green, right ventricle and pulmonary artery; and blue, CCS-lacZ staining. Ao indicates aorta; PA, pulmonary artery; and LV, left ventricle.
to the mitral-aortic continuity. In our patients, the arrhythmia was shown to originate from the MA-Ao junction itself. The present study suggests that triggered activity may be the underlying mechanism and that remnants of the developing conduction system may be the substrate for this form of atrial tachycardia. The much higher incidence of tachycardias originating from the MA-Ao in our patients when compared with the Kistler study cannot be readily explained. The fact that 50% of our patients were referred after a previous failed ablation may account for the difference. Therefore, our findings represent a selected group of patients and cannot be extrapolated to the general population of individuals with atrial tachycardia.

The MA-Ao Junction and the Developing Conduction System

Previous embryological studies have suggested that the occurrence of atrial arrhythmias at specific anatomic sites may be linked to the presence of the developing conduction tissue at these sites during embryogenesis. In the present comparative murine embryological study, the specialized conduction system was shown to run between the aorta and the AV canal early in the development. At a later stage (E 15), the staining of the conduction system was markedly reduced indicating regression of this system in older embryos. These findings represent a selected group of patients and cannot be extrapolated to the general population of individuals with atrial tachycardia.

Clinical Implications

Some patients with atrial tachycardia are refractory to anti-arrhythmic agents and require catheter ablation to eliminate the arrhythmia. Previous studies have shown that ablation is less successful at eliminating left atrial tachycardias compared with right atrial tachycardias. Knowledge of the most frequent sites of origin, including the MA-Ao junction, can facilitate successful ablation of these tachycardias.

Acknowledgment

The authors thank Melanie Fridell Ross, MSJ, ELS, for editing assistance. Linda Horne and Deanna Congdon provided excellent secretarial support.

References

Left Atrial Tachycardia Originating From the Mitral Annulus–Aorta Junction
Mario D. Gonzalez, Leonardo J. Contreras, Monique R.M. Jongbloed, Jaime Rivera, Timothy P. Donahue, Anne B. Curtis, Michael S. Bailey, Jamie B. Conti, Glenn I. Fishman, Martin J. Schalij and Adriana C. Gittenberger-de Groot

Circulation. 2004;110:3187-3192; originally published online November 8, 2004; doi: 10.1161/01.CIR.0000147613.45259.D1
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/20/3187

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/