REVIEW ARTICLE

A Reappraisal on Lidocaine-Sensitive Repetitive, Uniform Atrial Tachycardia

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Background: Lidocaine sensitive, repetitive atrial tachycardia is an unusual arrhythmia whose electrophysiologic substrate remains undefined. We aimed to analyze the electropharmacologic characteristics of this arrhythmia with emphasis on its cellular substrate and response to drug challenges.

Methods: We retrospectively analyzed a series of 18 patients from an electrocardiographic and electrophysiologic perspective and the response to pharmacological challenge.

Results: There was no evidence of structural heart disease in 12 patients, 4 patients presented with systemic hypertension; one patient had a prior myocardial infarction and one a mitral valve prolapse. The arrhythmia depicted a consistent pattern in nine patients. The first initiating ectopic beat showed a long coupling interval, the cycle length of the second atrial ectopic beat presented the shortest cycle length and a further prolongation was apparent towards the end of the atrial salvos. Conversely, in the other nine cases, the atrial tachycardia cycle length was erratic. The arrhythmia was suppressed by asynchronous atrial pacing at cycle lengths longer than those of the atrial tachycardia. Intravenous lidocaine eliminated the arrhythmia in all patients, but intravenous verapamil suppressed the atrial tachycardia in only two patients while adenosine caused a transient disappearance in 2/8 patients. Only one patient responded to all the three agents. Radiofrequency ablation was successfully performed in 10 patients.

Conclusions: Repetitive uniform atrial tachycardia can be sensitive to lidocaine. In few cases, this rare focal arrhythmia may be also suppressed by adenosine and/or verapamil, which suggests a diversity of electrophysiologic substrates that deserve to be accurately identified.

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Atrial tachycardias are a variety of supraventricular tachycardias that do not require the atrio-ventricular junction, accessory pathways, or ventricular tissue for initiation and perpetuation of the fast heart rhythm. The cardiac rate during atrial tachycardia encompasses a broad range (120–250 beats per minute); atrial rhythm is usually regular whereas ventricular rhythm may become irregular depending on the conducting properties of the atrio-ventricular node, which may give rise to

diverse conduction patterns (fixed or a combination of 2:1, 3:1, 4:1 atrio-ventricular conduction or Mobitz I periodicities). QRS complexes are usually narrow, unless bundle branch block aberration or ventricular preexcitation are also present.

The P-wave morphology may provide useful clues to determine the anatomic site of origin and, eventually, the intrinsic mechanism of the arrhythmia. However, it has a limited spatial resolution since atrial pacing at sites as far apart as

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32 mm in the coronary sinus and 17 mm in the right atrium causes morphologically identical P waves.¹

Atrial tachycardias may be classified on the basis of their clinical and electrocardiographic characteristics, the underlying electrophysiologic mechanisms and the anatomic site of origin.

Clinical sustained uniform atrial tachycardia is relatively infrequent; the prevalence in symptomatic patients is lower than 1%, while it accounts for around 10% in adults undergoing electrophysiological studies.² Bursts of atrial tachycardia are common in Holter ECG recordings of aged individuals. Repetitive, almost incessant, uniform atrial tachycardia that is a rare variety of the arrhythmia, described in detail in this review, accounts for only a 0.3% among all supraventricular tachycardias referred to our center for evaluation and treatment. Multifocal atrial tachycardia shows an atrial rate higher than 100 beats per minute, with at least three morphologically different P-waves, irregular P-P intervals and an isoelectric baseline between the P waves.

Based on endocardial activation, atrial tachycardias may be grouped into focal, arising from a localized area in the atria, and macroreentrant, most commonly occurring in patients with structural heart disease, particularly after surgery involving incisions, or scarring in the atria.

The three putative underlying electrophysiologic mechanisms of focal atrial tachycardia are enhanced automaticity, triggered activity, and microreentry.³⁻⁷ Although a significant overlap between the electrophysiologic characteristics of atrial tachycardias caused by triggered activity and microreentry is a limiting factor in the analysis of their mechanisms, a previous report showed that adenosine insensitive focal atrial tachycardias are caused by micro-reentry.⁷ Focal sustained atrial tachycardias are usually refractory to vagal stimulating maneuvers and some of them may be sensitive to adenosine and/or verapamil. Regarding long-term treatment, most antiarrhythmic agents, such as Class I A and I C sodium channel blockers, β adrenergic blockers and calcium channel blockers, have a very limited efficacy while Class III agents may provide better results.

Lidocaine, a class Ib antiarrhythmic drug has been used as a first line therapy for ventricular arrhythmias occurring in the setting of the acute myocardial infarction. Despite its negligible electrophysiologic effects on atrial, sinus node and atrio-ventricular nodal tissues, Cotoi and Luca⁸ showed more than three decades ago that lidocaine

may terminate diverse atrial tachyarrhythmias, and later, Markowitz et al.⁹ described a patient with a repetitive form of atrial tachycardia that was responsive to lidocaine.

In this manuscript we will revisit our findings regarding a very peculiar and rare variety of focal repetitive atrial tachycardia whose electrophysiologic substrate is still intriguing and it was shown to be highly sensitive to intravenous lidocaine and usually refractory to most other antiarrhythmic agents.^{10,11}

LIDOCAINE-SENSITIVE, RATE RELATED, REPETITIVE, UNIFORM ATRIAL TACHYCARDIA

This is a peculiar form of chronic, iterative, uniform atrial tachycardia whose unique electrophysiologic characteristics and pharmacologic responses might indicate an unusual arrhythmogenic mechanism operating in human atrial tissue. Since 1995 to the present we identified 18 cases of this arrhythmia, which were selected for this presentation from 24 patients referred for study of chronic, repetitive, uniform atrial tachycardias.

CLINICAL AND ELECTROCARDIOGRAPHIC CHARACTERISTICS

Clinical Findings

Table 1 depicts the main clinical characteristics of 18 patients with lidocaine sensitive, rate related, repetitive, uniform atrial tachycardia.

Sixteen patients complained about palpitations (associated with dizziness and a syncopal episode in one of them and with chest pain in another two); two patients were asymptomatic, and the arrhythmia was fortuitously diagnosed during a routine clinical examination. No evidence of structural heart disease was found in twelve patients (one of them had multiform ventricular premature beats), four patients suffered from systemic hypertension, one patient had a previous myocardial infarction, and the remaining one had a mitral valve prolapse. The B mode echocardiogram was normal in twelve patients and showed mild left ventricular dilation in two young patients, concentric left ventricular hypertrophy with mild left atrial enlargement in three hypertensive patients, and a typical mitral valve prolapse in one patient.

Table 1. Clinical Findings in Eighteen Patients with Repetitive Atrial Tachycardia

Case	Age (years)	Gender	Symptoms	ECG in Sinus Rhythm	B-Mode Echocardiogram	Antiarrhythmic Treatment
1	14	F	Palpitations	Normal	Normal	A, D, Fle, P, Q
2	16	M	Palpitations	Normal	Mild LV Dilation	A, At, Fle, Q, V
3	21	M	Palpitations	Normal	Normal	A, At, D, Fle, V
4	22	M	Palpitations	Normal	Normal	A, At, Fle, Q
5	24	F	Palpitations	Multiform PVC's	Mild LV Dilation	At, Fle, P, V
6	28	M	Palpitations	Normal	Normal	A, At, P
7	60	F	Asymptomatic	LVH	Mild LAE; Mild LVH	A, At
8	56	M	Asymptomatic	Inferior and Posterior Fibrosis	Normal	N
9	62	M	Palpitations	LVH	Mild LAE; Mild LVH	–
10	53	F	Palpitations	Normal	Normal	B, Fle, D
11	83	F	Palpitations	Normal	Mild LAE; Mild LVH	At, d,l sotalol, Fle
12	48	M	Palpitations	Normal	Normal	P
13	37	F	Palpitations	Normal	MVP	Digoxin, A
14	20	M	Palpitations	Normal	Normal	Fle, d,l sotalol
15	28	M	Palpitations	Normal	Normal	–
16	34	M	Palpitations	Normal	Normal	–
17	25	M	Palpitations; chest pain	Normal	Normal	–
18	19	M	Palpitations	Normal	Normal	Nevibolol, Iv

A = amiodarone; At = atenolol; B = bisoprolol; D = digoxin; D = diltiazem; F = female; Fle = flecainide; LAE = left atrium enlargement; LV = left ventricle; LVH = left ventricle hypertrophy; M = male; MVP = mitral valve prolapse; N = nadolol; P = propafenone; PVCs = premature ventricular contractions; Q = quinidine; S: d,l-sotalol; V = verapamil; Iv = ivabradine.

Electrocardiographic Findings

In all patients, the baseline ECG showed almost incessant bursts of self-limited atrial tachycardia (single or double atrial premature beats were infrequently observed) separated by one to three beats of sinus node origin (Fig. 1).

Duration of atrial tachycardia bursts was variable (between three or four beats and several seconds), even in the same patient, and most of them showed 1:1 AV conduction. Rate-related changes in the PR interval (due to P-P interval variations during the runs of atrial tachycardia) and, eventually, Mobitz type I atrioventricular block were observed. The arrhythmia exhibited a stereotyped pattern in nine patients. In fact, in all cases the initiating atrial ectopic beat had a relatively long coupling interval, whereas in those nine patients the cycle length of the second atrial premature beat was the shortest and a further prolongation was apparent to the end of atrial salvos (Fig. 2A and B). Conversely, in the other nine cases the atrial tachycardia cycle length showed erratic variations (Fig. 2C and D).

In addition, shortening of the sinus node cycle length induced by mild exercising suppressed or abbreviated the repetitive atrial discharges

while prolongation of the sinus node cycle length, obtained by vagal stimulating maneuvers, tended to prolong the bursts of ectopic atrial activity. These changes were not associated with any discernible modification in atrial tachycardia cycle length. Furthermore, the suppressive effect was consistently observed at sinus node rates slower than that of the atrial tachycardias. Thus, it was not due to an overdrive suppression mechanism.

The same relationship between the sinus node rate and the atrial ectopic activity was also clearly documented in 24-hour ECG Holter recordings performed in 12 of our patients. In fact, in nine of them the runs of atrial tachycardia were present when the sinus node rate was slow, or relatively slow, and disappeared or were abbreviated at higher sinus node rates. However, in three patients the arrhythmia was not only suppressed by moderate increments of sinus node rate but also by sinus node slowing during sleep, indicating that appropriate changes in cardiac rate that reflect the predominance of either the sympathetic or the vagal influences on the heart may have the same suppressing action on the arrhythmia mechanism. In no instance was the arrhythmia found to deteriorate into atrial flutter or fibrillation.

Figure 1. A typical example of iterative, uniform atrial tachycardia. Note that the bursts of ectopic atrial activity are separated by only one beat of sinus node origin. Numbers indicate the posttachycardia sinus node cycle length (with permission Ref. [10]).

The morphology and polarity of the ectopic P-waves suggested that the arrhythmia arose from disparate regions of the atria, a fact that was confirmed by radiofrequency ablation of the arrhythmia successfully performed in nine of these patients.

Electrophysiologic Studies

Seven patients underwent electrophysiologic evaluation. During the study, the arrhythmia showed the same patterns found during the electrocardiographic recordings. Two different patterns of repetitive atrial discharges were identified. In all the patients the coupling interval of the first atrial ectopic beat was relatively long and in five cases, the second cycle length was the shortest, and, thereafter, the cycle length showed a gradual prolongation until spontaneous termination of the arrhythmia. In another two patients, the cycle length of the ectopic atrial bursts was erratic,

thus clearly differing from the other cases (Fig. 2). The arrhythmia was not consistently altered by atrial premature impulses elicited by programmed pacing but was suppressed in every patient by asynchronous atrial pacing at cycle lengths longer than those of the atrial tachycardia (Fig. 3).

Moreover, a critically long atrial paced cycle length could be identified for arrhythmia resumption, under the form of progressively longer runs of atrial tachycardia as the paced cycle length was prolonged. Of note, in no instance could the arrhythmia be induced by atrial premature stimuli, while in the seven patients (100%) it reappeared immediately after discontinuance of atrial pacing with a pattern identical to that observed at baseline.

PHARMACOLOGIC RESPONSES

As seen in Table 1, most patients had been unsuccessfully treated orally with therapeutic

Figure 2. The different behavior of repetitive uniform atrial tachycardia cycle length. The coupling interval of the initiating beat is always relatively long; in A and B, the following cycle length is the shortest and then it shows a gradual prolongation until the end of atrial salvos, while in C and D the ectopic atrial cycle length is erratic. HRA = high right atrium electrogram. (with permission Ref. [10]).

doses of different antiarrhythmic agents, including β adrenergic blockers, sodium channel blockers (Class I A and I C), calcium channel blockers, d,l-sotalol, amiodarone, ivabradine, and digoxin. Intravenous lidocaine and calcium channel blockers were tested in all patients (verapamil in 17 patients and diltiazem in the remaining one) and intravenous adenosine was administered to 10 patients. Intravenous lidocaine (0.5–1.0 mg/kg in 1 minute) produced a rapid suppression of the arrhythmia (between 30 and 120 seconds after the end of injection) in all patients, an effect that persisted for 8–25 minutes and disappeared gradually. In no case was the suppression of the arrhythmia by lidocaine related to sinus node acceleration. In fact, sinus node rate during the peak effect of the drug was slower than the critical heart rate that consistently caused the arrhythmia disappearance in each of the seven patients who underwent an electrophysiologic study, and not a single atrial ectopic impulse was observed

during sinus node slowing by bradycardia-inducing maneuvers. Figure 4 depicts the interruption of the repetitive atrial ectopic discharges after lidocaine administration.

In contrast, intravenous verapamil (10 mg in 60 seconds) suppressed the arrhythmia in only two patients (Fig. 5) and was ineffective in fifteen patients; although a Mobitz type I and even repetitive AV block during the bursts of atrial tachycardia were documented in nine of them. At the time of atrial tachycardia termination, the sinus node cycle length did not differ from that at baseline and normal sinus rhythm still persisted at slower heart rates, and the arrhythmia was absent even after pauses lasting up to 1250 and 1620 ms, respectively, induced by vagal stimulating maneuvers. In these two patients, atrial ectopic activity resumed 15 and 25 minutes after verapamil administration. A quite unexpected response was observed in one patient after intravenous diltiazem administration. The repetitive e irregular salvos

Figure 3. Suppression of bursts of atrial tachycardia (left panel) by atrial overdrive pacing (right panel; S–S interval: 320 ms). Note that the atrial pacing cycle length is longer than the atrial tachycardia cycle length. HRA = high right atrium; HBE = His bundle.

of atrial tachycardia turned into a regular and persistent form of the arrhythmia that lasted for nearly half an hour.

Intravenous bolus of 12 mg of adenosine caused a rapid but ephemeral (lasting 12–25 seconds) disappearance of the arrhythmia in only three patients (Fig. 6), causing a brief shortening of atrial tachycardia (which turned into single and couplets of atrial ectopic activity) in one patient and was

ineffective in the other six patients, in whom a variable degree of AV block of the atrial ectopic impulses was documented without discernible changes in the arrhythmia cycle length (Fig. 7).

Taken as a whole, lidocaine-sensitive atrial tachycardia was also responsive to verapamil in only 2/17 patients (11.7%) and to adenosine in 3/10 patients (30%). Only one patient responded to all the three agents.

Figure 4. Suppressive effect of intravenous lidocaine on repetitive atrial tachycardia. Numbers (ms) correspond to atrial cycle length of the ectopic atrial discharges (upper panel). To be noted, restoration of normal sinus rhythm was preceded by a prolongation of atrial tachycardia cycle length (lower panel).

Figure 5. Upper tracings: Repetitive atrial tachycardia at baseline was eradicated by intravenous lidocaine (1 mg/kg). Lower tracings: Intravenous verapamil (10 mg), administered after reappearance of the arrhythmia with identical characteristics as at baseline, were also effective. Note that only isolated atrial premature beats still persisted one minute after the verapamil injection and normal sinus rhythm was present 2 minutes later. (with permission Ref. [11]).

UNDERLYING MECHANISMS

The electrophysiologic mechanism operating in lidocaine-sensitive atrial tachycardia is challenging. In our initial manuscript on this topic,¹⁰ we described that the electropharmacologic characteristics were not consistent with delayed afterdepolarizations, re-entry or abnormal automaticity. In fact, in addition to the irregular cycle length, the arrhythmia could neither be consistently induced nor terminated by programmed premature atrial stimulation, which, although not totally exclusive, was strong evidence against a re-entrant mechanism. Bursts of atrial tachycardia were favored (lasted longer) or even triggered by slowing down the intrinsic heart rate. Besides,

they were systematically suppressed by atrial pacing at relatively short cycle lengths although longer than those of the atrial tachycardia, a finding that is inconsistent with the presence of delayed afterdepolarizations. However, it should be stressed that Markowitz et al.⁹ reported four patients with repetitive uniform atrial tachycardia in whom the arrhythmia was suppressed by adenosine and verapamil, and therefore attributed to delayed afterdepolarizations. Lidocaine was tested in only one of these four patients and was also effective to suppress the atrial tachycardia.

Taking into account the preceding considerations we propose an entirely speculative mechanism in which early afterdepolarizations, described in the M ventricular cells¹² or atrial re-excitation

Figure 6. Transient suppression of atrial tachycardia bursts by intravenous adenosine (12 mg). Upper panel: red arrow points to the onset of a period of stable sinus rhythm. Lower panel: 30 seconds after adenosine administration, a premature atrial beat occurs (gray arrow) and the next sinus beat (black arrow) is followed by reappearance of a run of atrial tachycardia.

due to local differences of membrane potential might play a mechanistic role. In fact, early afterdepolarizations were found to be dependent on long cycle lengths¹³ and abolished by mexiletine.¹⁴

However, transient suppression of the arrhythmia by intravenous verapamil and/or adenosine, as demonstrated in 11–33.3% of our patients, strongly suggests that triggered activity due to delayed afterdepolarization may play a mechanistic role. No information is available on the effects of lidocaine on atrial-delayed depolarizations. However, Sicouri et al.¹⁵ have shown that ranolazine, a sodium channel blocker, abolished triggered activity caused by delayed afterdepolarization in

preparations of pulmonary vein sleeves. Thus, in cases in which the arrhythmia was suppressed not only by lidocaine but also by adenosine and/or verapamil, triggered activity caused by delayed afterdepolarizations might have been the operating cellular mechanism. Remarkably, lidocaine has a much lesser degree of atrial selectivity than other sodium channel blockers.¹⁶

The underlying electrophysiologic substrate of iterative uniform atrial tachycardias that responded only to lidocaine still remains obscure. The focal characteristics suggested by the radiofrequency ablation of the arrhythmia in discrete sites of the right atrium might be due to a local re-excitation

Figure 7. Repetitive atrioventricular block during the bursts of atrial ectopic activity after a 12 mg intravenous adenosine injection in a patient with lidocaine-sensitive, iterative atrial tachycardia. HRA = high right atrium; HBE = His bundle. (with permission Ref. [11]).

mechanism, such as the one proposed above. A distinctive characteristic of lidocaine sensitive atrial tachycardia lies on its repetitive, almost incessant, character, which precludes an accurate assessment of the effects of programmed atrial pacing on initiation and interruption of the arrhythmia and therefore its full electrophysiologic exploration.

It is noteworthy that not all repetitive atrial tachycardias are lidocaine sensitive. In fact, lidocaine failed to suppress the arrhythmia in six of our primary group of 24 patients. In four of these patients, the atrial tachycardias were insensitive not only to lidocaine but also to adenosine and verapamil; in one patient both adenosine and verapamil suppressed the arrhythmia, while the remaining one was only sensitive to adenosine.

LONG TERM MANAGEMENT

Antiarrhythmic Drugs

In three symptomatic patients, the arrhythmia was treated with mexiletine (360 mg twice a day orally) with excellent clinical outcomes. Persistence of only isolated and infrequent atrial premature contractions were documented in repeated ECG Holter recordings in two of these patients during a follow up of 6 and 30 months, respectively.

Also only one of the two patients in whom intravenous verapamil suppressed the arrhythmia responded to oral verapamil while the other patient was efficaciously controlled with amiodarone, during 18 months and 34 months follow up, respectively. In both cases, occasional isolated atrial premature beats were found during follow up in repeated 24-hour ECG Holter monitoring. One patient was lost of follow-up after failing to flecainide.

Two asymptomatic patients received no further antiarrhythmic treatment, and their clinical, electrocardiographic and echocardiographic conditions remained stable after a 6 month and a 2-year follow-up, respectively.

Intriguingly, in one patient the atrial tachycardia ceased spontaneously and was absent in repeated ECG Holter recordings after being persistent during a 30 month follow up.

Radiofrequency Ablation

Radiofrequency ablation of the arrhythmia was successfully performed in 10 symptomatic patients. The atrial ectopic foci were ablated in the lateral wall of the right atrium at a high/medium level in three cases, in the high posterior right atrium in two patients (Fig. 8), in the body of the right atrial appendage in two patients, in the low septal right atrium in one patient, in the proximity of the mitral annulus in one patient and in the

Figure 8. 3-D activation mapping (En Site Array, Navex, St Jude) of the right atrium in a patient with lidocaine-sensitive atrial tachycardia who underwent radiofrequency ablation of the ectopic focus. This was located at a high level of the posterior wall of the right atrium (crista terminallis). Coded colors, from white to violet, indicate the spread of atrial impulse. Brown circles indicate sites where radiofrequency energy was delivered leading to suppression of the arrhythmia. AT = tricuspid valve; IVC = inferior vena cava; SVC = superior vena cava.

fosa ovalis region in the remaining one. The atrial electrograms recorded at the successful sites preceded the onset of the ectopic P waves by 20–45 ms. No specific relationship could be established between the site of atrial tachycardia origin and the pharmacologic responses. No atrial tachyarrhythmias were documented on repeated 24-hour ECG Holter recordings during follow-up periods between 12 and 40 months.

CONCLUSIONS

Many repetitive uniform atrial tachycardias seem to be sensitive only to lidocaine, a sodium channel blocking agent with a predominant action

at the ventricular level. However, in some cases, this rare focal arrhythmia may be also suppressed by adenosine and/or verapamil suggesting a diversity of electrophysiologic substrates. In addition studies in larger populations with repetitive uniform atrial tachycardias are necessary to determine the full electrophysiologic and pharmacologic responses of these arrhythmias to gain better knowledge of the different electrophysiologic mechanisms involved in their origin.

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