Acceleration of Typical Atrial Flutter Due to Double-Wave Reentry Induced by Programmed Electrical Stimulation

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Background—Acceleration of reentrant tachycardia induced by programmed electrical stimulation is a well-documented phenomenon, but the mechanisms remain poorly understood.

Methods and Results—Twelve patients with typical atrial flutter were studied. Activation sequence of the underlying reentrant circuit was recorded by multiple multipolar electrodes placed in the right atrium. In five patients, 27 episodes of atrial flutter acceleration were induced by single extrastimuli delivered in the isthmus between the tricuspid annulus and eustachian ridge (TA-ER isthmus) and one by rapid overdrive atrial pacing. Analyses of the activation sequences, intracardiac electrograms, and 12-lead surface ECG P-wave morphology indicated that the acceleration was caused by two successive activation wave fronts circulating in the same direction along the same reentrant circuit (double-wave reentry, DWR). DWR was induced only within a narrow range of coupling interval, from 2 to 45 ms beyond the effective refractory period, and was associated with unidirectional antidromic block of the paced impulse. Patients with DWR had a shorter effective refractory period (138.8±13.4 versus 163.8±12.2 ms, P<.015) and larger excitable gap (124.0±22.6 versus 83.2±13.2 ms, P<.009) compared with patients without inducible DWR. All of the DWR episodes were transient. Most (78.6%) terminated after one of the double wave fronts was blocked in the TA-ER isthmus.

Conclusions—DWR is one of the mechanisms responsible for programmed electrical stimulation-induced atrial flutter acceleration in human subjects. Its induction requires a sufficient excitable gap and antidromic unidirectional block of the paced impulse in the TA-ER isthmus. In addition, the TA-ER isthmus is the usual site of DWR termination.

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Key Words: atrial flutter ■ reentry ■ tachycardia ■ electrical stimulation

It is well recognized that reentrant tachycardias such as typical AFL can be transiently entrained and terminated by overdrive pacing. They can also be accelerated by overdrive pacing. However, our understanding of the mechanisms responsible for such acceleration in humans remains incomplete. Using a rabbit model, Brugada et al first described that acceleration of reentrant VT induced by PES may result from the presence of two successive activation wave fronts traveling in the same direction in the same reentrant circuit, that is, DWR. The most persuasive evidence for DWR in their studies was derived from high-resolution epicardial mapping that revealed an identical activation sequence during tachycardia acceleration compared with baseline VT. Frame et al demonstrated that DWR was responsible for pacing-induced acceleration of reentrant tachycardia around the tricuspid annulus in a canine atrial preparation. However, there has been no human study to date with direct mapping of the activation sequence along the reentrant circuit to support DWR as a mechanism responsible for reentrant tachycardia acceleration. The purpose of this study was to test whether DWR could be induced in patients with typical AFL and to describe the electrophysiologic mechanism underlying this phenomenon.

Methods

Patient Selection
Twelve consecutive patients with typical AFL who were referred for ablative therapy were studied between September 1996 to March 1997. Eleven were men, and the average age was 65.8±13.7 years (range, 35 to 79). Eleven patients had chronic counterclockwise typical AFL for at least 1 month and one had recurrent paroxysmal typical AFL. Three patients had stable coronary artery disease, one had moderate mitral regurgitation, three had cardiomyopathy with left ventricular ejection fractions ranging from 35% to 45%, and two had hypertension. The remaining patients did not have structural heart disease. All had normal thyroid function. None had clinical evidence of significant myocardial ischemia. None were taking antiarrhythmic medications or digitalis before the study.

Electrophysiological Testing
All patients were admitted to the Electrophysiology Laboratory in a postabsorptive, unsedated state after informed consent was obtained. Venous accesses were secured with 8F sheaths that were inserted in the usual fashion in the right internal jugular vein and the femoral
Induction of Typical AFL

Eleven patients had chronic counterclockwise typical AFL. In one patient with paroxysmal AFL, AOD pacing was used to induce AFL.

Stimulation Protocol

Once the catheters were successfully deployed, the flutter cycle length was measured and the pacing threshold in the TA-ER isthmus was determined. The diagnosis of typical AFL was then confirmed by concealed entrainment from the TA-ER isthmus.

Single AES, at twice the diastolic pacing threshold with a pulse width of 2 ms, were delivered in the TA-ER isthmus through the distal pair of electrodes of the ablation catheter. The timing or coupling interval of the AES was progressively decreased at 5- to 10-ms decrements to scan the entire AFL cycle. The atrial ERP in the TA-ER isthmus was defined as the longest AES coupling interval that failed to result in an atrial depolarization. The excitable gap was determined as the range of coupling intervals that advanced local activation in the TA-ER isthmus and reset AFL. AOD pacing in the TA-ER isthmus was then performed in an attempt to terminate AFL. The pacing interval was selected to be 20 to 50 ms below the AFL cycle length. Aggressive rapid atrial pacing was performed in one patient only to avoid induction of atrial fibrillation. In three of the five patients with induced AFL acceleration, ibutilide, 2 mg over 15 minutes, was infused and the above stimulation protocol was repeated.

After the study protocol, patients underwent radiofrequency AFL ablation in the usual fashion. The study protocol was approved by the Institutional Review Board of UCSF Medical Center.

Statistical Analysis

All statistical analyses were performed with commercially available software (Excel 4.0 Microsoft Corp). All variables are reported as mean ± SD. Comparison between means was performed with two-tailed t test. A value of P < .05 is considered statistically significant.

Results

In 11 patients with chronic AFL, the surface ECG showed negative flutter waves in the inferior leads (II, aVF, and III) associated with counterclockwise endocardial activation around the tricuspid annulus. AFL was induced in one patient with paroxysmal AFL who had predominantly positive flutter waves in the inferior surface ECG leads and a clockwise endocardial activation sequence. The participation of the TA-ER isthmus as part of the reentry circuit during AFL was confirmed by entrainment pacing in all patients. The baseline AFL cycle length was 259.1 ± 28.7 ms. The ERP and excitable gap determined from TA-ER isthmus was 151.3 ± 17.9 and 103.6 ± 27.7 ms, respectively.

Induction of AFL Acceleration by PES

A total of 28 episodes of acceleration of typical counterclockwise AFL were observed in five patients. All had chronic typical counterclockwise AFL. Twenty-seven episodes were induced by single AES and one was induced by rapid AOD pacing.

Induction of AFL acceleration with AES depended on the coupling interval. An AES introduced late in the flutter cycle resulted in bidirectional propagation, collision with the previous AFL wave front, and tachycardia resetting (Fig 2). Very early AES simply fell in the atrial ERP. A critically timed AES, within a time window of 2 to 45 ms after the TA-ER isthmus ERP, reproducibly induced AFL acceleration in five patients (Fig 3A). The mean AES coupling interval that resulted in AFL acceleration was 159.5 ± 20.0 ms. The difference between the coupling intervals that induced AFL...
When AFL acceleration was induced, there was always acceleration and the ERP was 19.9±13.2 ms (range, 2 to 45 ms). When AFL acceleration was induced, there was always propagation of the AES-induced local depolarization in the orthodromic direction and block of the impulse in the antidromic direction within the TA-ER isthmus (Fig 3B). Therefore, collision with the wave front of the previous AFL cycle did not occur and its propagation was allowed to continue. This resulted in two successive wave fronts traveling in the same reentrant circuit simultaneously (DWR).

Induction of AFL acceleration with AES also depended on the ERP and excitable gap in the TA-ER isthmus. In the remaining seven patients in whom AFL acceleration was not observed, all AES resulted in either bidirectional propagation (3.0±1.8 beats per episode). The ratio of accelerated AFL cycle length to the baseline AFL cycle length (ACL/BCL ratio) was 70.4±3.8% (range, 60.5% to 75.7%). Significant variation in cycle length was always present during AFL acceleration, although the identical activation sequence was maintained (Figs 3 and 5, 6, and 7). During the AFL acceleration, local activation at two distant anatomic sites occurred almost simultaneously within the same reentrant circuit (Figs 3 and 5 to 7). This finding clearly cannot be explained by a single but rapid activation wave front because of the physical distance and the significant baseline conduction time required for impulse propagation to travel between these two sites.

Termination of PES-Induced AFL Acceleration

Twenty-two of 28 episodes (78.6%) of DWR were terminated after one of the double wave fronts was blocked in the TA-ER isthmus (Figs 3, 6, and 7). There was always progressive conduction delay in the TA-ER isthmus before the block. Four episodes observed in three patients were interrupted by early or "premature" local activations in the inferolateral right atrium that failed to propagate orthodromically (Fig 5). The remaining two episodes were interrupted by AES that resulted in local capture in the TA-ER isthmus. These local captures were blocked orthodromically and resulted in antidromic collision with one of the DWR wave fronts. Termination of DWR led to resumption of stable counterclockwise typical AFL in 25 of 28 episodes (90%). However, a more complete match of the flutter waves in all 12 leads (Fig 3A). Both findings indicated that the activation wave fronts traveled along the same reentrant circuit during both the acceleration and the spontaneous typical AFL. All episodes of acceleration were transient, ranging from 2 to 11 beats (3.0±1.8 beats per episode). The ratio of accelerated AFL cycle length to the baseline AFL cycle length (ACL/BCL ratio) was 70.4±3.8% (range, 60.5% to 75.7%). Significant variation in cycle length was always present during AFL acceleration, although the identical activation sequence was maintained (Figs 3 and 5, 6, and 7). During the AFL acceleration, local activation at two distant anatomic sites occurred almost simultaneously within the same reentrant circuit (Figs 3 and 5 to 7). This finding clearly cannot be explained by a single but rapid activation wave front because of the physical distance and the significant baseline conduction time required for impulse propagation to travel between these two sites.
complex rapid irregular right atrial rhythm developed after the determination of DWR in the remaining three episodes, one of which eventuated in atrial fibrillation.

In one patient, attempts were made to induce AFL acceleration by delivering the AES in the isthmus, at the CS os, and low lateral right atrium anterior to crista terminalis. The same protocol was executed in the TA-ER isthmus, at the CS os, and at the low lateral right atrium. Two episodes of acceleration were induced with a single AES delivered in the TA-ER isthmus, eight episodes were induced with a single AES delivered at the CS os, but none was seen with AES delivered at the low lateral right atrium (Fig 8). The ERP determined at these three sites were only slightly different (TA-ER isthmus, 160 ms; CS os, 155 ms; lower lateral right atrium, 170 ms), and the AFL cycle length remained stable throughout the study (270 to 275 ms).

In three of the five patients who demonstrated AFL acceleration at baseline, ibutilide infusion did not terminate AFL immediately, and we were able to determine the ERP and excitable gap in the TA-ER isthmus during AFL 10 to 20 minutes after ibutilide infusion. No AFL acceleration was inducible with AES after administration of ibutilide. In these three patients, the ERP was increased (from 132 to 180 ms, from 129 to 179 ms, and from 144 to 247 ms, respectively). The excitable gap was decreased by >30 ms after ibutilide infusion (from 145 to 113 ms, from 104 to 71 ms, and 152 to 88 ms, respectively). The excitable gap as a percentage of AFL cycle length dropped from 52.4% to 38.4%, from 44.6% to 28.4%, and from 51.4% to 26.3%, respectively. In the remaining two patients with DWR, ibutilide was not given because AOD terminated AFL in one and led to atrial fibrillation in the other.
Discussion

Mechanism of Tachycardia Acceleration

The most important finding of this study is the demonstration of DWR as an explanation of tachycardia acceleration in patients with AFL. Our data are perfectly consistent with those derived from prior animal studies describing DWR. In brief, a critically timed impulse was shown to result in antidromic block within the TA-ER isthmus but was associated with orthodromic propagation and the tachycardia accelerated with identical electrogram morphology. We also found that DWR was only found in patients with large excitable gaps, was site dependent, and could be abolished by ibutilide, an agent that increased refractoriness and decreased the excitable gap. Before our hypothesis is accepted, several other potential mechanisms should be discussed. Conceivably, other reentrant mechanisms could be responsible for acceleration. This could include a mechanism in which the isthmus is still critical to the circuit but the remainder of the circuit is "short circuited" to give a shorter tachycardia path length. Alternatively, the acceleration may be due to an entirely different circuit of smaller size, leaving the tricuspid annulus as a bystander, with passive activation from a smaller dominant circuit. The arguments against either of these hypothesis include: (1) no changes in the flutter wave morphology in the surface 12-lead ECG recordings were found between DWR and typical flutter; (2) electrogram morphology along the annulus was very similar if not identical to the spontaneous flutter; and (3) the finding of simultaneous activation of two portions of the reentrant circuit. Clearly, simultaneous local activation cannot be explained on the basis of a single wave front.

Figure 5. Termination of DWR by a premature depolarization. DWR was initiated with a critically timed AES that resulted in orthodromic propagation and antidromic block without collision with the flutter wave front of the previous cycle. AFL cycle length was 275 ms. Coupling interval was 143 ms and ERP was 132 ms. The premature atrial depolarization resulted in antidromic propagation, as evidenced by premature local activation at TA 1 with a different electrogram morphology and collision with one of the double wave fronts. However, the premature depolarization failed to propagate orthodromically and thereby led to termination of DWR acceleration and resumption of the single-wave typical AFL. Hollow arrows at the top point to simultaneous local activations at CS os and TA 1.
Another possibility that should be considered involves the notion that atrial premature stimulation during AFL served to initiate a new automatic or triggered rhythm within the original flutter circuit. Several of the observed features appear to mitigate against such focal mechanisms and include: (1) automatic rhythms are seldom initiated or terminated by single premature complexes; (2) the mode of initiation and termination of acceleration was critically dependent on block in the TA-ER isthmus, an observation strongly supportive of reentry; and (3) the activation sequence during acceleration and progressive isthmus conduction delay would force one to construct an unlikely hypothesis of abnormal automaticity or triggering with constant unidirectional block in the isthmus, and termination of the rhythm was always fortuitously associated with conduction delay in the TA-ER isthmus.

**Determinants of Initiation and Maintenance of DWR**

The TA-ER appears to be critical for both initiation and maintenance of DWR. Our observations are in accord with those of Olgin et al demonstrating that the isthmus was the usual site of block in the initiation of typical AFL. In addition, DWR (best observed in longer episodes) was always associated with increasing conduction delay in the isthmus before isthmus block. This supports the previous observations by Frame et al with a canine tricuspid ring model. The anatomic and electrophysiologic configurations leading to isthmus block are not clear. According to Wang et al, the inferoposterior portion of the cristae terminalis thins as it courses toward the os of the coronary sinus and gives out delicate branches to the internal bundle. The TA-ER isthmus

**Figure 6.** DWR induced by rapid atrial overdrive. In one patient (patient 1), rapid atrial overdrive pacing during typical counterclockwise AFL induced DWR. A, Spontaneous AFL cycle length was 300 ms. The atrial pacing interval was 100 ms. B, The last pace stimulus resulted in capture, orthodromically initiating one of the double waves (dashed arrow). The other wave front (solid arrow) was derived from the penultimate driven atrial complex. As in DWR induced with single AES, the activation sequence and electrograms are essentially identical during the acceleration and typical AFL. There was progressive conduction delay (underscored numbers) in the TA-ER isthmus before block of one of the double wave fronts that led to reversion to single wave typical AFL. The cycle length variation was again apparent. Hollow arrows at the top point to simultaneous local activations at two distant sites (CS os and TA 2).

**Figure 7.** Longest recorded episodes of AFL acceleration caused by DWR. These tracings were recorded in patient 11. The AFL cycle length was 242 ms. The ERP was 129 ms and the AES coupling interval was 142 ms. The typical pattern of DWR was illustrated by (1) rapid and irregular rhythm with identical activation sequence and electrogram morphology compared with spontaneous AFL, (2) simultaneous local activation of two distant sites in the circuit (hollow arrows at CS os and TA 1) during acceleration, and (3) progressive conduction delay before block of one of the double waves in the TA-ER isthmus.
DWR was first described by Brugada et al., with a rabbit VT model composed of a thin ring of ventricular myocardium around a fixed central obstacle created by cryoablation. In this model, VT acceleration caused by DWR was induced by use of up to seven extrastimuli, delivered during the reentrant VT in 6 (23%) of the 26 experiments. The activation sequence determined by high-resolution epicardial mapping was identical during DWR compared with the baseline VT. Preparations in which DWR was induced had significantly longer VT cycle length, shorter ERP, and longer excitable gap both in absolute terms and as a percentage of the VT cycle length. Our data are comparable to their findings. However, DWR acceleration was more sustained, and significant cycle length variation during DWR was absent in their ventricular preparation.

Frame et al.[17] extended these observations and demonstrated overdrive pacing induction of DWR in both atrial tricuspid and ventricular mitral annular ring tissue in a canine model. They showed, consistent with our observations in humans, that DWR was always transient in the atrium and that DWR terminated (with block of one wave front) into typical single-wave reentry. In addition, they showed that DWR was consistently associated with cycle length oscillations, which was possibly due to either unevenly spaced wave fronts or to the alternation in recorded monophasic action potentials. The DWR/atrial flutter cycle length ratio in their study ranged from 56% to 77%, which is similar to that found in our study (60.5% to 75.7%).

Comparison With Previous Studies

DWR was reproducibly induced with PES from either the TA-ER isthmus or the os of the coronary sinus but never from the low lateral right atrium. In each instance, stimulation from the latter site resulted in collision and reset, whereas stimulation from the former sites produced unidirectional isthmus block and DWR induction. This observation again highlights the critical role of the isthmus in DWR induction.

We also found that the magnitude of the excitable gap/tachycardia cycle length was well correlated with inducibility of DWR. It makes intuitive sense to believe that patients with larger excitable gaps will be better able to "accommodate" two reentrant waves. In support of this observation was the finding that ibutilide decreased the excitable gap (increased the atrial refractory period) and abolished DWR. This observation is in accord with the previous studies of Brugada et al.,[14] who showed that administration of a class III agent (RP6271a) prolonged ERP more than tachycardia cycle length decreased the excitable gap, and suppressed DWR in a rabbit ventricular tachycardia model. More recent studies by Reiter et al.[22] and Boersma et al.[23] further confirmed the suppressive effects of class III agents on inducibility of DWR.

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Clinical Implications

DWR, which uses the same reentrant circuit as the typical AFL, is an arrhythmia that may be suspected on the basis of several pathognomonic features. These include development of transient acceleration and oscillation of the flutter rate with P-wave morphology identical to that of typical flutter on surface 12-lead ECG recordings. With intracardiac recordings, one can document that the electrogram morphology is identical to the spontaneous flutter, that the initiation and termination occurs with isthmus block, and that there is simultaneous activation of two sites in the circuit.

Recently, Kalman et al.24 summarized the current definition of atrial flutter rhythms. In their terminology, atypical AFL is described as a rapid rhythm with significant cycle length variation, which may prove to be prefrillibrilatory. DWR as described will clearly fit under the atypical flutter rubric. It is anticipated that as our knowledge increases, many more types of these accelerated flutter-like rhythms will further clarify the spectrum of atypical AFL. In addition, whereas DWR appears to be a transient arrhythmia for the vast majority of patients, in three episodes (10%), termination of DWR was followed by more complex atrial arrhythmias and even atrial fibrillation. Hence DWR may be one mechanism for conversion of stable AFL into more complex atrial arrhythmias.

Limitations

The transient nature of DWR precluded the use of entrainment pacing from various sites to prove involvement in the tachycardia circuit. We attempted to circumvent this problem by use of underdrive pacing (Fig 3) but were sometimes left with the uncertainty of whether "pacing-induced" block in the isthmus was spontaneous or related to subthreshold stimulation. On four occasions, a spontaneous atrial premature depolarization terminated the acceleration. This premature activity always occurred in the low lateral right atrium. The paucity of mapped sites did not allow us to decide whether the premature activity was due to random ectopic atrial activity or echo wave25 or perhaps was related to a break in the line of block, as has been suggested as a mechanism of termination for canine flutter and VT.26,27 All of the patients with inducible DWR had typical counterclockwise AFL. We cannot extrapolate our results to those with with heptanol, class Ic and class III drugs on reentrant ventricular tachycardia: a model for the excitability gap for the inducibility of double-wave reentry. Circulation. 1994;90:1012–1022.


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