Evidence for Transient Linking of Atrial Excitation During Atrial Fibrillation in Humans

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Background. Atrial fibrillation is usually thought of as a "random" pattern of circulating wavelets. However, local atrial activation should be influenced by the constant anatomy and receding tail of refractoriness from the previous activation. The general tendency for wave fronts to follow paths of previous excitation has been termed "linking." We examined intra-atrial electrograms recorded during atrial fibrillation for evidence of linking.

Methods and Results. Two minutes of atrial fibrillation were recorded in 15 patients with an orthogonal catheter. We have previously demonstrated that this catheter can be used to detect changes in the direction of local atrial activation. A mean vector was calculated for each electrogram. The similarity of the direction of the vectors from two consecutive electrograms can be quantified on a scale of 1 to -1 by calculating the cosine (cos) of the smallest angle (θ) between them. Two vectors pointing in the same or opposite directions then have cos(θ) = 1 or -1, respectively. For the entire group of patients, mean cos(θ) was significantly greater than 0 (mean, 0.36; p < 0.001). In nine of 15 patients, there were groups of six or more consecutive beats (total, 44 groups; range, six to 14 beats per group) in which the direction of activation of each beat was within 30° of the previous beat. The likelihood of one group of six or 14 consecutive similar beats occurring by chance in any one patient in 1 minute is <0.05 and <0.000001, respectively. There was a significant correlation (r=0.90) between the amount of linking during the first and second minutes of atrial fibrillation in each patient.

Conclusions. Transient similarities in the direction of wavelet propagation in the majority of patients with atrial fibrillation is consistent with the presence of transient linking. To our knowledge, this is the first direct evidence that atrial activation during atrial fibrillation in humans is not entirely random. (Circulation 1992;86:375–382)

Key Words • mapping • catheters • atrial fibrillation

Atrial fibrillation is often described as a disorganized or "random" phenomenon,1–3 yet it has been shown to exhibit many features that suggest an underlying order. Electrophysiological properties of the atria dependent on anatomy, for example, anisotropic conduction and cellular uncoupling, should remain constant during atrial fibrillation. The power spectrum of atrial fibrillation has been shown to have a discrete peak in the 4–9-Hz band.4 This peak has been shown to change in response to administration of antiarrhythmic drugs.5 In a recent preliminary mapping study, Allesie et al6 reported qualitatively that wavelets tended to enter areas that were previously activated by another fibrillatory wave. Further, Shimizu et al7 reported that the onset of induced atrial flutter in the canine pericarditis model was preceded by a brief episode of a transitional rhythm with the characteristics of atrial fibrillation. During this brief episode of atrial fibrillation, the interpreted direction of wavelet propagation followed the tail of the receding activation until block occurred. These qualities of atrial fibrillation do not seem consistent with random activation.

The tendency for wave fronts to follow paths of previous excitation is well known. The term "linking" was first used by Rosenbaum8 to describe this phenomenon for the specific case of the perpetuation of functional bundle branch block caused by repetitive transseptal retrograde concealed penetration of impulses along the contralateral bundle branch. This term was later expanded by Lehmann et al9 to include any scenario in which "the fate of each impulse entering a macroreentrant circuit is functionally linked to the electrophysiological sequelae of the previous beat." Lehmann et al hypothesized that the dynamic maintenance of functional block caused by repeated collision or interference of a wave front with impulses from competing pathways was the mechanism for preferential conduction along one limb of a macroreentry circuit. The term "linking" has always been used to describe this phenomenon in well-defined anatomic pathways,8–10 e.g., the His-Purkinje system or the atrioventricular bypass tract of patients with Wolff-Parkinson-White syndrome. There is no reason, however, to think that linking would need a predefined pathway to occur. The anatomic and electrophysiological constraints of
the atrium could create a path of preferential conduction that could be dynamically maintained by interference of competing impulses at the wave front edge. This would create a preferred route of conduction in the path of the previous activation. Chen et al.\(^1\) have observed that shortly after electrical induction of ventricular fibrillation, “[ventricular fibrillation] is not totally random but frequently follows similar, gradually changing pathways.” Thus, atrial fibrillation, in which each wavelet is constantly encountering refractory tissue because of previous excitation, is an excellent substrate in which linking could occur. However, this organization of impulses has not been described.

We have previously reported the use of an orthogonal catheter to measure the relative direction of local atrial endocardial activation.\(^12\) If atrial fibrillation were truly a random process, then the direction of activation of successive wavelets past the catheter tip should be random. It was our first hypothesis that the direction of activation of successive wavelets past the catheter tip would not be random. Furthermore, because of the distribution of refractoriness left by the receding tail of the previous wavelet and functional block of competing pathways by the wave front edge, we hypothesized that each wavelet would be more likely to follow a path of previous excitation than expected by chance, i.e., linking would occur.

**Methods**

Fifteen consecutive patients in atrial fibrillation undergoing cardiac catheterization were included in the study. Diagnosis of atrial fibrillation was based on the surface ECG using the following criteria: no discrete p waves in any surface lead and wide waves that were irregular in timing and morphology at a rate greater than 350 beats per minute. The patients’ ages ranged from 49 to 79 years (mean, 66 years). The protocol for this study was approved on October 3, 1989, by the Evanston Hospital Institutional Review Board for the protection of human subjects.

**Orthogonal Catheter**

To compute the relative direction of local atrial endocardial activation, an orthogonal catheter previously described by our laboratory\(^12\) was used. Two standard ring-sensing electrodes were located 1 and 4 mm from the catheter tip, respectively, and were used as the x lead for orthogonal recordings. Four additional electrodes were located circumferentially around the catheter midway between the two ring electrodes, with a bipole size of 2 mm. Opposite pairs of these circumferential electrodes were used to record the y and z leads for orthogonal recordings. This configuration was manufactured by Webster Inc. (Baldwin Park, Calif.) on a 6F catheter. Because the exact orientation of the electrodes with respect to the atrium was unknown but fixed in a given study, the direction of activation of successive wavelets can be compared within the same patient but not in any direct relation to the anatomy of the heart.

**Data Acquisition**

For each patient, an introducer sheath was inserted into the femoral vein using the Seldinger technique. The orthogonal catheter was advanced under fluoroscopy and placed against the endocardial wall of the high right atrium. Firm and stable contact with the endocardium was confirmed before each recording and reconfirmed at the end of each recording.

At least 1 minute of atrial fibrillation was recorded from each patient. Surface leads I, II, and V\(_1\) and the three orthogonal intra-atrial leads were filtered (0.05–5,000 Hz), amplified, and recorded by an electrophysiological recorder (Honeywell VR16; Electronics for Medicine, Honeywell Inc., Pleasantville, NY.) and stored on FM tape (Honeywell 101; Electronics for Medicine).

**Signal Processing**

The stored data were played back through a low-pass antialiasing filter with a cutoff frequency of 120 Hz. Signals were then gain and digitized at 1,200 Hz on a Macintosh IIci computer (Apple Computer, Cupertino, Calif.). A recursive digital high-pass filter with a cutoff frequency of 15 Hz was used to remove baseline wander and low-frequency atrial repolarizations present in the signal. Although the peak in the power spectrum of atrial fibrillation lies in the 4–9-Hz band,\(^4\) this band contains the fundamental frequency or rate information in the fibrillatory signal (rate of 350 beats per minute = 5.8 Hz). The shape and relative timing information used to construct vector loops were contained in higher frequency bands not removed by the filter.

**Mean Vector**

The mean vector was then calculated for each electrogram in each patient. Using vectorcardiographic techniques, it is possible to compute a three-dimensional vector loop for each electrogram. A vector sum over the appropriate region of the depolarization complex would then yield a single vector representing the mean direction of each vector loop.

Fibrillatory electrograms were detected using a modification of the Pan and Tompkins ORS detection algorithm.\(^13\) Each lead (x, y, and z) was differentiated, squared, and then smoothed with a moving window integrator. The resulting x, y, and z signals were then combined so that peak detection was not dependent on any one lead. A variable threshold was applied to the combined signal using hysteresis and a blanking period of 8 msec after the offset of each electrogram to avoid double counting of electrogams. The resulting signal is a stream of pulses, with each pulse corresponding to the timing and duration of each electrogram in the minute of data (Figure 1). Pulses that were longer than 100 msec in duration were skipped, as they represent physiologically untenable electrograms and are probably short areas of fractionated activity.

With the timing and duration of each electrogram computed, the mean vector of each electrogram can be calculated as previously described by our laboratory.\(^12\) To establish a fiducial point in the center of the vector loop, a point was chosen at the half-area vector location of the loop, i.e., the point that best separated the loop into two equal halves.\(^14\) The mean electrogram vector was then calculated by summing each of the three-dimensional vectors over a 17.5-msec window (21 data points) centered at this point. The 21-point window was chosen because it is long enough to cover the prominent portion of each electrogram and short enough so that the mean was not “removed” by the high-pass filter.
FIGURE 1. Example of the Pan and Tompkins QRS detection algorithm modified for use with fibrillatory electrograms. X(t), Y(t), and Z(t) are each segments of raw data recorded from the respective leads of the orthogonal catheter during atrial fibrillation. Each signal is passed through a 15-Hz high-pass filter, differentiated, squared, and passed through a moving window integrator. The three resulting signals are then summed to give signal F(X,Y,Z). Variable thresholds placed over signal F(X,Y,Z) result in a stream of pulses marking the timing and duration of each electrogram as seen in signal P(X,Y,Z).

**Cos(θ) Plot**

The similarity in the direction of mean vectors from successive electrograms can be quantified on a scale of 1 to −1 by calculating the cosine of the smallest angle (θ) between them. If two vectors are pointing in the same direction, then the angle between them is 0°, and \( \cos(\theta) = 1 \). If two vectors are pointing in opposite directions, then the angle between them is 180°, and \( \cos(\theta) = -1 \). If the two vectors are perpendicular, then \( \cos(\theta) = 0 \). Thus, \( \cos(\theta) \) will range between 1 and −1, with 1 indicating similarity and −1 indicating opposition. A plot of \( \cos(\theta) \) versus vector pair clearly shows trends in mean vector direction (Figure 2). A group of vectors pointing in the same direction can easily be identified as a group of points near 1. Furthermore, if the mean vector direction were random throughout the entire minute of data, points would be distributed equally above and below 0, so the mean \( \cos(\theta) \) would not be significantly different from 0.

Examples of \( \cos(\theta) \) plots for sinus rhythm, atrial flutter, and atrial fibrillation are shown in Figure 3.

**Direction of Linking**

We hypothesized that linking caused by a constant anatomic or pathological condition would result in a similar vector direction each time linking occurred. On the other hand, linking caused by transient functional properties of atrial propagation might exhibit a different vector from episode to episode. Therefore, in each patient with multiple episodes of linking, the direction of these episodes was studied to determine if there were any preferred directions of linking in each patient or among patients.

**Cycle Length**

Increased local organization of atrial activation might also be reflected in the cycle length of electrograms. With repeated activation along a similar pathway during linking, one might expect a longer and/or less variable cycle length than during nonlinked episodes. For each episode of linking occurring in each patient, we chose the next equally long group of beats for comparison. Mean cycle length and cycle length variance were compared among the patients for the linked versus nonlinked groups of beats.

**Two Simultaneous Orthogonal Recordings**

In three patients, a second orthogonal lead was introduced into the mid right atrium. Simultaneous orthogonal recordings were made to investigate the relation of linking at different sites in the atria.

**Additional Recordings**

To examine whether the presence or absence of linking was a characteristic of certain patients or only of certain times in each patient, additional segments of

![Figure 2](image-url)
beats with \( \cos(\theta) \) greater than 0.866. There was a total of 44 such runs in these nine patients, ranging from six to 14 electrograms in duration. The likelihood of a single run of 14 consecutive such beats occurring by chance in any one patient during a 1-minute recording is less than one in 30 million.

An episode of linking occurring in patient 10 is shown (Figure 5). Note the similar morphology of the electrograms corresponding to the area of high \( \cos(\theta) \) and the change in morphology corresponding to the decrease in \( \cos(\theta) \). The cycle length during this period varied from 110 to 170 msec.

**Direction of Linking**

Of the nine patients with episodes of linking, one had a single episode of linking, and eight had multiple episodes during a 2-minute recording. In four of the eight patients with multiple episodes of linking, the

**Results**

Mean \( \cos(\theta) \) ranged from 0.02 to 0.76 (mean, 0.36) in the 15 patients. For the entire group of patients, mean \( \cos(\theta) \) was significantly greater than 0 \( (p<0.001) \) (Figure 4).

FiguRe 4. Mean values of \( \cos(\theta) \) are shown for each of the 15 patients. Note that in each patient, mean \( \cos(\theta) \) is greater than 0, and that for the entire group of patients, mean \( \cos(\theta) \) is significantly greater than 0 \( (p<0.001) \).
linking always occurred in approximately the same
direction in a given patient. However, as would be
expected, there was no consistent direction of linking
from patient to patient. In the four remaining patients,
linking occurred in multiple directions (Figure 6).

**Cycle Length**

The mean cycle length of the linked versus nonlinked
episodes was not significantly different among the pa-
tients (mean ± SD, 159 ± 17 versus 157 ± 17 msec). The
variability in cycle length was significantly less for the
linked versus nonlinked groups (mean ± SD variance,
122 ± 44 versus 392 ± 149 msec; p < 0.001).

**Two Simultaneous Orthogonal Recordings**

In each of the three patients from whom we had two
simultaneous orthogonal recordings, mean cos(θ) was
significantly greater than 0 at both sites. Two patients
who had three and six statistically significant episodes of
linking at one site had 18 and 11 episodes of linking at
a second site, respectively. Episodes of linking at one
site did not consistently coincide in time with episodes
of linking at the second site. One patient who had no
significant episodes of linking at one site had two
significant episodes of linking at the second site.

**Additional Recordings**

There was a significant correlation between the num-
ber of episodes of linking at each site during the first
and second minutes of atrial fibrillation (r = 0.90) (Table
1). In the six patients who showed no evidence of
linking, analysis of a second segment of data again
showed no evidence of linking in any patient at the same
site. Of the eight patients in whom linking occurred in
the first minute, six also showed evidence of linking in the
second minute. Two did not have any episodes of six
or more consecutive similar beats in the second minute.

In the three patients with simultaneous orthogonal
recordings at a second site, the number of episodes of
linking was roughly consistent from one minute to the
next at the second site.

**Clinical Correlation**

In the 10 patients in whom echocardiograms were
available, we found no significant correlation between
left atrial size and the number of episodes of linking
(r = 0.2).

**Discussion**

This study, to our knowledge, provides the first direct
evidence that atrial activation during atrial fibrillation in
humans is not random. Given the constant anatomy,
including the orifices of the venae cavae, the tricuspid
valve, and the coronary sinus os, the myocardial fiber
orientation, cellular uncoupling, and fibrosis, the finding
of evidence of nonrandom activation patterns in atrial
fibrillation is not unexpected. These structures must
constrain wave front propagation by creating preferred
routes of conduction and by promoting the development
of arcs of functional block around which successive
invading impulses may propagate. Thus, although the
determinants of activation patterns during atrial fibril-
lation may be complex, they are influenced by certain
predictable organizing constraints. Transient linking, as
demonstrated in this study and as often occurs during
other, simpler cardiac rhythms, is one manifestation of
these constraints.

Because some patients appeared to demonstrate evi-
dence of linking and some did not, we examined our
data further to determine whether linking at a specific
site is always present or absent or, conversely, if it
occurs only from time to time at that site. The former
could be a consequence of the constant anatomy of the
atrium, whereas the latter pattern could reflect tran-
sient functional properties of atrial electrophysiology.
Wells et al.17 recording from a single bipolar epicardial
lead, found that the "discreteness" of the fibrillatory
signal during atrial fibrillation often changed from mo-
moment to moment, appearing more or less organized at
different times and at different atrial sites. We found
that the amount of linking at one atrial site during 1
minute was a good predictor of the amount of linking in
the next minute. Whether there is greater variation in
the amount of linking over longer time periods is not
addressed by our study.

In patients with two simultaneous orthogonal record-
ings, the amount of linking was consistent from one
minute to the next at a single site but not between
different sites (e.g., Table 1, patient 11). This implies
that linking may not occur at all sites in the atrium. In a

**Figure 5.** Top panel: Plot of cos(θ)
versus vector pair for 1 minute of atrial
fibrillation. Bottom panel: Orthogonal
electrograms corresponding to the area
between the arrows. Note the similar mor-
phology of the electrograms corresponding
to the area of high cos(θ) above and the
change in morphology corresponding to
the drop in cos(θ) toward the right of the
arrow. The cycle length during this period
varied between 110 and 170 msec.
given patient, there may be some sites in which linking readily occurs and others in which it is less likely, perhaps because of the local atrial anatomy or pathology. When linking occurred at two atrial sites, it did not necessarily occur simultaneously. That is, there was not evidence of a global increase in the organization of atrial fibrillation. The discordance in timing of the episodes of linking that occurred at two different sites was expected given that fibrillation is characterized by an absence of any constant temporal relation between different sites.  

It is also possible that linking could be patient specific. For example, patients with more severe atrial disease might be less likely to demonstrate linking. We could not reach any conclusion about this from examining only one or two sites in each patient. There was no correlation between the number of episodes of linking at a single site and echocardiographic left atrial size. The great variation in the amount of linking from site to site might obscure such a relation if it exists; multisite mapping could better determine the presence or absence of linking in patients with differing atrial pathology.

When multiple episodes of linking occurred, we determined whether the wave front direction was similar each time linking occurred. Linking caused by a constant atrial anatomy would be expected to have a relatively constant direction from episode to episode (or perhaps a direction 180° opposite). Conversely, linking caused by functional atrial electrophysiological properties might well be associated with differing vector directions for different episodes. In our data, both patterns were seen. In the patients with linking in multiple directions, there were often episodes of linking in roughly opposite directions. This makes a strong argument for an anatomic component to linking. On the other hand, episodes of linking occurring in varied directions (Figure 6, patient 8) suggest that transient electrophysiological properties also may play a role in linking.

One of the distinctive features of atrial fibrillation is the irregularity in cycle length of atrial electrograms. If repeated activation along similar pathways was occurring transiently during atrial fibrillation, one might expect this to be reflected in either a less variable or longer cycle length. The decrease in the variability of cycle lengths we found during episodes of linking supports the notion that these episodes are more "organized" than other nonlinked times. The transient preferred routes of conduction we propose, however, did not appear to significantly lengthen the mean time between activations.

Allesie et al.  have reported that during atrial fibrillation, "it is exceptional that an impulse follows the same circular route more than once." Our results do not contradict this finding. The presence of linking does not mean that a single wavelet is continually reentering the same path. To the contrary, linking reflects the tendency for successive wavelets to continually follow the same path because of the distribution of refractoriness and functional block of competing pathways.

Study Limitations

Vectors calculated from orthogonal electrograms are not likely to quantify exactly the direction of wavelet propagation. Differences in the surface area, bipole size, and distance from the endocardium of the x versus the y and z electrodes might bias the calculated vector. Although catheter bias could explain the overall mean \( \cos(\theta) \) being significantly greater than 0, this influence would be uniform throughout all the recordings. It would therefore be difficult to explain the wide variation in \( \cos(\theta) \) among the patients, from 0.01 to 0.71, and the transience of episodes of high \( \cos(\theta) \) in each patient by catheter bias alone. The episodes of linking occurred in multiple directions in some patients, were site specific, and had no particular preference toward any one absolute direction among the patients. Thus, catheter bias is an untenable exclusive explanation for the linking we observed.

Another limitation of this study is the difficulty in calculating mean vectors from fibrillatory electrograms.
Although most of the recorded electrograms were discrete because of firm electrode contact with the endocardium and close bipolar spacing, a few patients had short areas of fractionated activity, which made analysis difficult. In addition, the mean vector calculated from some bizarre vector loops undoubtedly represented the composite direction of several fractionated wavelets colliding near the catheter. We assumed, however, that such occurrences would result in successive mean vectors with no apparent pattern and thus would not create the false appearance of linking. Indeed, there were no episodes of linking including the aforementioned anomalies.

Although we interpreted our data with the multiple wavelet hypothesis of atrial fibrillation in mind, triggered activity or reentry of a wavelet during atrial fibrillation could result in similar findings. Our results do not address whether the multiple wavelet hypothesis or triggered activity is the mechanism of atrial fibrillation, but rather identify transient periods of organized, nonrandom activity. Because we are able to examine only one or two sites at a time, we are blinded to the activation pattern of the rest of the atrium. Multisite mapping will help to further elucidate the mechanism by which this organization occurs.

The presence of at least six consecutive electrograms with \(\cos(\theta)\) greater than 0.866 was used to identify episodes of linking that were unlikely to occur by chance alone. This should in no way be regarded as a minimum criterion for linking. Linking could occur at a length of two, three, four, or five beats in duration. However, we felt it was necessary to ensure that the linking we measured was not a chance event. Although a more liberal criterion for linking could have been established, we felt it more prudent to use a strict criterion for this initial study.

### Conclusions

From our data, one cannot predict the direction of propagation of any wavelet past a fixed point of atrial endocardium given the direction of propagation of the previous wavelet. However, the occurrence of transient similarities in the direction of wavelet propagation in the majority of patients with atrial fibrillation is consistent with the presence of transient linking and, therefore, is evidence that activation during atrial fibrillation is not entirely random. Further study of the phenomenon of linking is necessary to determine its role in the pathophysiology of atrial fibrillation.

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