JACC Vol. 6, No. 1
July 1985:119–23

Independent and Interactive Effects of Digoxin and Quinidine on the Atrial Fibrillation Threshold in Dogs

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To assess the effects of digoxin as single therapy and in combination with quinidine in the treatment of atrial fibrillation, the atrial fibrillation threshold was determined from the right atrial appendage and Bachmann's bundle in 11 open chest dogs. In group 1 (six dogs), the atrial fibrillation threshold was determined at baseline, post-quinidine (10 mg/kg intravenously) and then post-digoxin (50 μg/kg intravenously). In group 2 (five dogs), the order of drug administration was reversed.

The results of this study were: 1) Digoxin had no significant effect on the atrial fibrillation threshold when given alone. 2) Quinidine significantly increased the atrial fibrillation threshold ($p < 0.002$) and the addition of digoxin resulted in a further increase in threshold ($p < 0.002$). 3) Quinidine produced greater suppression of atrial fibrillation induction at the right atrial site than at the Bachmann's bundle site, suggesting differential effects of quinidine on atrial fibers.

(J Am Coll Cardiol 1985;6:119–23)

Digitalis has been used for many years in the treatment of atrial fibrillation. Although it is well known that digitalis slows the ventricular response in patients with atrial fibrillation, its effect on the atrial arrhythmia itself remains controversial. Several investigators (1,2) believe that frequently digitalis will convert atrial fibrillation to normal sinus rhythm. Others (3–5) believe that because of the vagal effects of digitalis, the refractory period of atrial muscle is decreased and this may tend to perpetuate atrial fibrillation. Some authors (6,7) believe that if digitalis does have the ability to convert atrial fibrillation to normal sinus rhythm, it does so by improving the overall hemodynamics. In a recent study by Weiner et al. (8), conversion to normal sinus rhythm occurred with the administration of digoxin alone in 85% of episodes of atrial fibrillation after a median of 4 hours. Most episodes were terminated before significant slowing of the ventricular response was noted. However, it is not known whether digoxin facilitated conversion to normal sinus rhythm because the study did not include an untreated control group. Engel and Gonzalez (9) found that the vulnerable zone for inducing repetitive atrial beats was reduced by ouabain and they believed that this indicated a protective effect of digitalis against atrial fibrillation and flutter. In the present study we further evaluated the effects of digitalis on atrial fibrillation by studying in dogs the antifibrillatory action of digoxin when used alone and in combination with quinidine.

Methods

Experimental preparation. Eleven healthy mongrel dogs (weight 17 to 21 kg) were sedated with sodium thioamylal (15 mg/kg) and then anesthetized with intravenous chloralose (60 mg/kg). The dogs were intubated and ventilated with a Harvard respirator using room air. A heating blanket was used to maintain normal body temperature. The heart was exposed with a mid-sternal incision and suspended in a pericardial cradle. The sinus node was crushed to allow for right atrial pacing at a constant interval of 400 ms in all dogs without competition from the sinus node. This was performed because Han et al. (10) observed that in the dog there is a greater temporal dispersion of recovery of atrial excitability at slow than at faster heart rates. This, in turn, could predispose to arrhythmias. Therefore, in this experiment the heart rate was kept constant.

Pacing was accomplished with a bipolar plunge electrode in the right atrial appendage. All stimuli were delivered by a programmable stimulator (Bloom Associates). Bipolar plunge electrodes were placed in the right atrial appendage,

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0735-1097/85/$3.30

Table 1. Atrial Fibrillation Threshold in Group 1*

Dog	From Bachmann's Bundle			From Right Atrial Appendage		
	Baseline	Quinidine	Quinidine + Digoxin	Baseline	Quinidine	Quinidine + Digoxin
1	6.5	10.4	19.4	16.4	>100	>100
2	9.3	14.7	24.0	>100	>100	>100
3	8.8	17.7	20.9	6.5	>100	>100
4	4.8	8.8	14.9	15.8	>100	>100
5	3.1	7.5	11.5	3.2	>100	>100
6	1.6	5.1	11.0	5.7	>100	>100
Mean ± SD	5.7 ± 3.1	10.7 ± 4.7	17.0 ± 5.3	9.5 ± 6.1	>100	>100
		p < 0.002	p < 0.002			

*Thresholds are given in mA. Thresholds >100 mA indicate noninducibility of atrial fibrillation.

left atrial appendage and Bachmann's bundle to record local atrial electrograms. An Electronics for Medicine DR-8 recorder was used to record surface and local electrograms.

Determination of atrial fibrillation threshold. For the induction of atrial fibrillation, two unipolar plunge electrodes were placed 5 mm apart in the right atrial appendage and also in the region of Bachmann's bundle. After nine paced beats from the right atrial appendage at a cycle length of 400 ms, atrial fibrillation was induced by delivering a train of impulses (2 ms pulse width, 10 ms interval) lasting 150 ms to either the right atrial appendage or Bachmann's bundle at the peak of the P wave of the ninth beat. Current was delivered by a constant current source capable of delivering current up to 100 mA, and the atrial fibrillation threshold was determined by increasing the current until atrial fibrillation was produced. Atrial fibrillation was defined arbitrarily as rapid, irregular atrial activity of 8 seconds' duration or longer. The atrial fibrillation threshold was determined three times at each site and is expressed as a mean of these three values.

Drug administration. In six dogs (group 1), the baseline atrial fibrillation threshold was determined from the right atrial appendage and Bachmann's bundle. The atrial fibrillation threshold stimulation protocol took approximately 5 minutes to complete at each site. Intravenous quinidine gluconate (10 mg/kg body weight) was then administered over 20 minutes and after a 5 minute interval the atrial fibrillation threshold was again determined at each site. Intravenous digoxin (50 μg/kg) was then added over 5 minutes, and after a 30 minute interval the atrial fibrillation threshold stimulation protocol was again repeated. In another five dogs (group 2), the order of drug administration was reversed. The half-time for elimination of intravenous quinidine is approximately 6 hours (11).

Statistical analysis. The atrial fibrillation threshold is expressed as mean ± SD. Statistical analysis was performed using a two-tailed Student's *t* test for paired data and also a two-tailed Fisher's exact test.

Results

Group 1 (quinidine followed by digoxin) (Table 1, Fig. 1). From Bachmann's bundle, atrial fibrillation could be induced in all six dogs during the baseline study. The mean atrial fibrillation threshold was 5.7 ± 3.1 mA at baseline and increased to 10.7 ± 4.7 mA after the administration of quinidine ($p < 0.002$). The mean atrial fibrillation threshold was further increased to 17.0 ± 5.3 mA ($p < 0.002$) after the addition of digoxin.

Figure 1. Results from group 1. **A**, Atrial fibrillation threshold from Bachmann's bundle. **B**, Atrial fibrillation threshold from the right atrial appendage. B = baseline; D = digoxin; Q = quinidine.

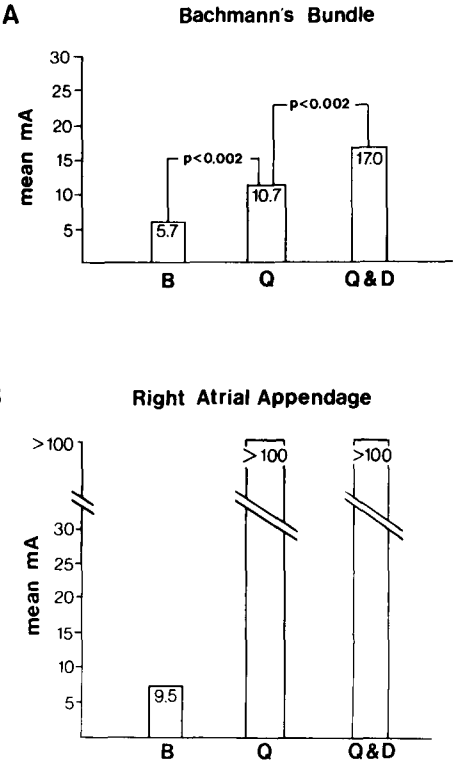


Table 2. Atrial Fibrillation Threshold in Group 2*

	From Bachmann's Bundle			From Right Atrial Appendage		
Dog	Baseline	Digoxin	Digoxin + Quinidine	Baseline	Digoxin	Digoxin + Quinidine
1	7.1	9.4	12.9	>100	>100	>100
2	5.6	7.7	>100	6.9	6.8	>100
3	8.8	6.2	21.7	14.4	7.3	>100
4	7.8	4.4	11.9	4.1	5.0	>100
5	4.5	5.5	16.1	4.6	4.2	>100
Mean ± SD	6.8 ± 1.7	6.6 ± 2.0	15.7 ± 4.4	7.5 ± 4.8	5.8 ± 1.5	>100
	p = NS		p < 0.04	p = NS		

*Thresholds are given in mA. Thresholds >100 mA indicate noninducibility of atrial fibrillation.

From the right atrial appendage, atrial fibrillation could be induced in five of the six dogs at baseline but could no longer be induced in any of the dogs after the administration of quinidine up to 100 mA. This remained unchanged with the addition of digoxin.

Group 2 (digoxin followed by quinidine) (Table 2, Fig. 2). Atrial fibrillation could be induced from Bachmann's bundle in all five dogs during baseline study. The mean atrial fibrillation threshold was 6.8 ± 1.7 mA at baseline and was essentially unchanged at 6.6 ± 2.0 mA (p = NS) after the administration of digoxin. After the addition of quinidine, the mean atrial fibrillation threshold increased to 15.7 ± 4.4 mA ($p < 0.04$). In Dog 2, atrial fibrillation could not be induced after the addition of quinidine up to 100 mA, and this sample was deleted during statistical analysis.

From the right atrial appendage, atrial fibrillation could be induced in four of the five dogs during baseline study. In these four dogs, the mean atrial fibrillation threshold was 7.5 ± 4.8 mA at baseline and there was no significant change after the administration of digoxin (5.8 ± 1.5 mA, p = NS). With the addition of quinidine, atrial fibrillation could no longer be induced from the right atrial appendage using up to 100 mA in all dogs.

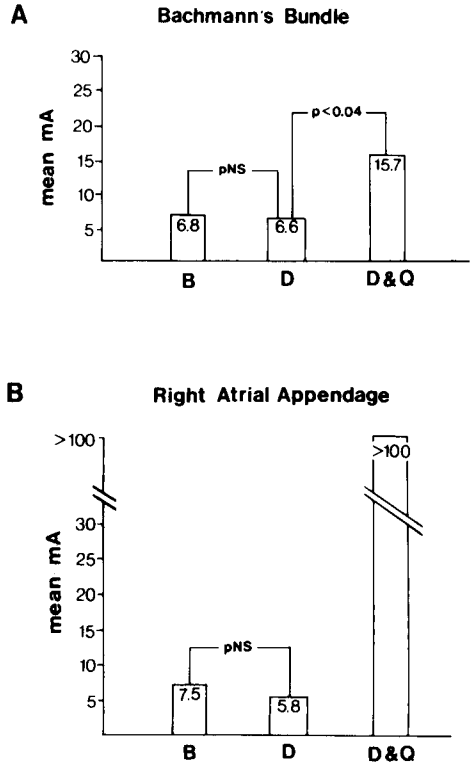
Inducibility. From the Bachmann's bundle site, atrial fibrillation remained inducible after the administration of quinidine alone (group 1) and in combination with digoxin (group 2) in 10 of the 11 dogs. From the right atrial appendage site, atrial fibrillation could not be induced after quinidine alone (group 1) or in combination with digoxin (group 2) in any of the nine dogs with inducible arrhythmia at baseline. This difference in inducibility was statistically significant ($p < 0.001$). An example of atrial fibrillation induction during baseline study is shown in Figure 3.

Discussion

The primary purpose of this study was to determine the effect of digoxin on the atrial fibrillation threshold of open chest anesthetized dogs. Our results demonstrate that digoxin has no effect on the atrial fibrillation threshold when used alone but exerts a significant synergistic effect on this threshold when used in combination with quinidine. Therefore, it appears that digoxin adds protection against experimentally induced atrial fibrillation when added to quinidine but not when given alone.

Possible mechanism of action. The mechanism of action by which digoxin increased the atrial fibrillation threshold after quinidine administration but not when given alone is not known. The action of digitalis on atrial tissue is

Figure 2. Results from group 2. **A**, Atrial fibrillation threshold from Bachmann's bundle. **B**, Atrial fibrillation threshold from the right atrial appendage. B = baseline; D = digoxin; Q = quinidine.



JACC Vol. 6, No. 1
July 1985:119–23

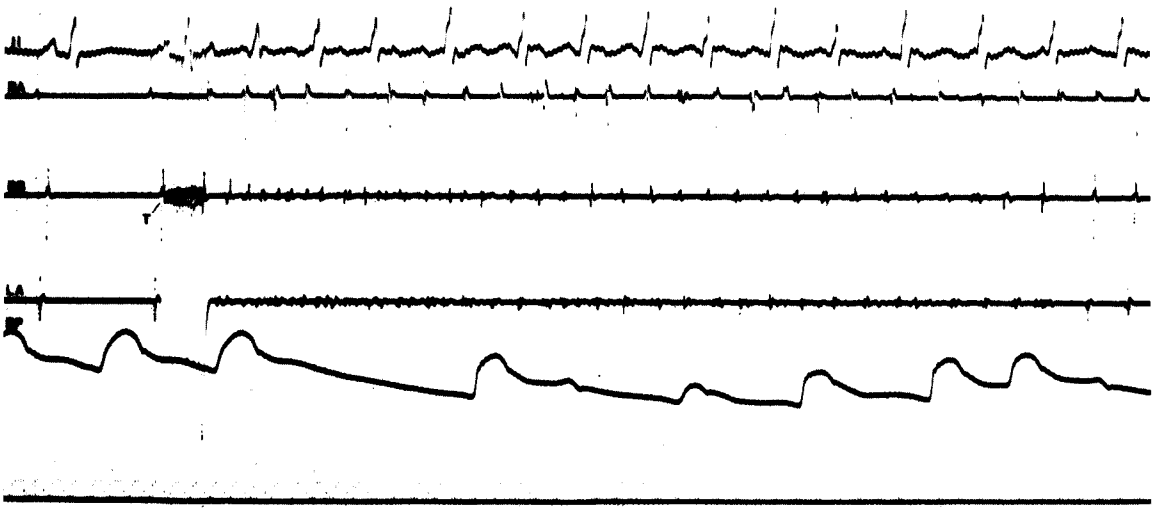


Figure 3. Induction of atrial fibrillation by delivering a train of rapid impulses (T) to the Bachmann's bundle site during a baseline study. From **top to bottom**, Electrocardiographic lead II, right atrial electrogram (RA); atrial electrogram from Bachmann's bundle (BB); left atrial electrogram (LA); blood pressure (BP).

complex and includes both a direct effect on the myocardium and indirect effects mediated through the autonomic nervous system (12). The direct myocardial effect increases the refractory period and slows conduction in atrial tissue. This increase in conduction time and refractory period would tend to be protective against atrial fibrillation. The indirect effect of digitalis is primarily vagally mediated and results in a decrease in atrial refractoriness that could precipitate or perpetuate atrial fibrillation. The effects of digitalis on the autonomic nervous system have been reviewed by Gillis et al. (13).

In our study, when digoxin was given alone it was possible that these opposing effects of digitalis on the atrium counterbalanced each other and the net effect was that no significant change was seen in the atrial fibrillation threshold. The increase in the atrial fibrillation threshold seen when digoxin was given after quinidine could be explained by the vagolytic effect of quinidine. This may oppose the vagal effects of digoxin, and the direct action of digoxin may predominate and result in a further increase in the atrial fibrillation threshold.

Differential effect of quinidine on atrial fibers. Also seen in this study was a marked difference in the inducibility of atrial fibrillation from the right atrial site compared with the Bachmann's bundle site after the administration of quinidine. After quinidine, atrial fibrillation could be induced in all but one dog from the Bachmann's bundle site (although at a higher atrial fibrillation threshold) but could not be induced in any of the dogs from the right atrial site. This indicates that although quinidine suppresses atrial fibrillation induction from both sites, this suppression was much greater at the right atrial site than at Bachmann's bundle. This differential effect may occur because fibers in Bachmann's bundle differ from ordinary atrial muscle in that they possess electrophysiologic characteristics similar to ventricular Purkinje fibers (14).

Clinical implications. The fibrillation threshold is considered a measure of the electrical stability of the myocardium. In general, there is correlation between the effect that a drug has on the fibrillation threshold and its antifibrillatory effect seen clinically. In this study, quinidine resulted in a significant increase in the atrial fibrillation threshold in dogs. This is in agreement with the clinical observation that quinidine is effective in maintaining normal sinus rhythm in patients with atrial fibrillation (15,16), and also with the observation that the prevention of atrial fibrillation by quinidine in patients during programmed atrial stimulation predicts the lack of clinical recurrences of atrial fibrillation on a long-term basis (17). Our study also demonstrates that digoxin has no significant effect on the atrial fibrillation threshold when given alone but does increase this threshold when used in combination with quinidine. Although it is difficult to extrapolate data from an animal model and apply it to the clinical setting, it suggests that the combination of digoxin and quinidine would be more effective than quinidine alone in maintaining normal sinus rhythm in patients with atrial fibrillation.

Limitations of study. The atrial fibrillation threshold is defined in this experiment as a single value, implying that the stimulus intensities below this level would never result in atrial fibrillation whereas atrial fibrillation would always occur with higher stimulus intensities. It is possible that the atrial fibrillation threshold may not be such a sharply defined value, but, rather, stimulus intensities above or below this value would be more or less likely to induce atrial fibrillation. Thus, the idea of an all or none phenomenon may not be realistic. Nevertheless, the atrial fibrillation threshold as defined in this study does give valuable infor-

mation as to the relative changes in the stimulus intensities required to induce atrial fibrillation before and after drug administration.

For the purpose of this experiment, atrial fibrillation was arbitrarily defined as rapid, irregular atrial activity of at least 8 seconds' duration. It is recognized that the ability to initiate and sustain fibrillation for this period of time may be a reflection of the intensity of the stimulus that initiates this chaotic rhythm and also the ability of the atrium to maintain this activity. It is conceivable that the higher atrial fibrillation threshold obtained after quinidine administration is a manifestation of both a higher intensity stimulus needed to initiate atrial fibrillation and also a decreased ability of the atrium to maintain atrial fibrillation for this arbitrary period of time. The relevance to the clinical situation, however, is the same in that it is only the sustained arrhythmia that is clinically important.

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