Failure of Beta-Adrenergic Blockade to Alter Ventricular Fibrillation Threshold in the Dog

EVIDENCE FOR EXTRA-ADRENERGIC EFFECTS OF PRONETHALOL

By Robert A. Rosati, B.S., James A. Alexander, M.D., Andrew G. Wallace, M.D., Will C. Sealy, M.D., and W. Glenn Young, Jr., M.D.

ABSTRACT

The effects of two beta-adrenergic blocking agents, pronethalol and propranolol, on ventricular fibrillation thresholds were tested in dogs. Pronethalol (4.0 mg/kg, 5 dogs) produced a mean increase of 45% in the fibrillation threshold. Propranolol (0.4 mg/kg, 7 dogs) failed to produce a significant change of the fibrillation threshold. To examine the possibility that the difference between the responses to pronethalol and propranolol might be related to the difference in dose of the beta-blocking agents, 4.0 mg/kg of propranolol was given to 3 dogs; this dose also failed to produce a consistent change of ventricular fibrillation threshold. These data indicate that under the conditions of our experiments it was possible to block the beta-adrenergic receptors with propranolol without producing a change of the ventricular fibrillation threshold. The increase of the fibrillation threshold produced by pronethalol was probably a consequence of its quinidine-like properties rather than of its beta-receptor blockade.

ADDITIONAL KEY WORDS

electrophysiology of the heart arrhythmias sympathetic nervous system catecholamines multiple responses vulnerability quinidine-like properties

Daggett and Wallace (1) recently reviewed the evidence that the autonomic nervous system is an important factor in the genesis of certain disturbances of cardiac rhythm. Arrhythmias can be produced by stimulation of the cardiac sympathetic nerves (2), by combined stimulation of the vagus and sympathetic nerves (3), by infusions of epinephrine (4), by the introduction of drugs into the fourth ventricle of the brain (5), and by stimulation of regions of the hypothalamus (6, 7). Han et al. (8) demonstrated that stimulation of cardiac branches of the left stellate ganglion increased the nonuniform pattern of recovery of excitability in ventricular muscle and resulted in a significant decrease of the threshold for ventricular fibrillation. Inhibition of sympathetic activity by beta-adrenergic blocking agents abolished arrhythmias produced by stimulation of the sympathetic nerves (9) or an overdose of digitalis (10, 11), and these agents seem to show considerable promise in reducing the incidence of ventricular fibrillation in patients with myocardial infarction (12). Although it seems logical to ascribe the antiarrhythmic properties of beta-receptor antagonists to their antiadrenergic effects, it is known that certain of these agents also have quinidine-like properties. This study was designed to evaluate the effects of beta-adrenergic blockade on the threshold for ventricular fibrillation. In order...
to gain greater insight into their mechanism of action, two agents were tested, only one of which has significant quinidine-like effects.

Methods

Twelve mongrel dogs ranging in weight from 11 to 15 kg were anesthetized intravenously with thiamylal sodium\(^1\) (10 mg/kg), intubated and ventilated with a Harvard respirator. Supplementary doses of the anesthetic were given as needed. A thoracotomy was performed in the fifth intercostal space on the right side. The pericardium was opened and the heart was suspended loosely in a pericardial sling. A bipolar surface electrode was sutured to the right atrial appendage for pacing and a bipolar test electrode was implanted in the atrioventricular groove. The test electrode consisted of two 25-gauge needles 1 cm apart embedded in a thin, flexible, silicone-rubber plaque.

Stimuli for pacing the heart and for testing the threshold of ventricular fibrillation were derived from a series of Tektronix 161 pulse generators that were programmed to pace the atrium at a basic frequency and to deliver a test pulse to the ventricle after every sixth basic response. Each pulse generator triggered a Grass stimulator that delivered the actual pulses to the heart through isolation units. The sinus node was crushed to slow the intrinsic heart rate and the atrium was then paced to maintain a constant beat rate. The ECG was monitored on a Tektronix 561-A oscilloscope.

The experimental procedure was as follows. With the test stimulus set to occur well after the end of the refractory period, its amplitude was increased until a propagated ventricular response was produced. The least amount of current required to induce fibrillation by a single pulse timed to occur during the vulnerable period was designated the ventricular fibrillation threshold (VFT). The hearts were defibrillated within 30 sec and 15 min were allowed to elapse for restoration of a steady state\(^1\). VET and VFT were then determined a second time. During the second determination the amplitude of the test pulse was increased by 2- to 3-ma steps through a range which encompassed the previously determined fibrillation threshold so that a more exact estimate of VFT could be made. In most instances, these two determinations agreed within 2 to 3 ma. If they did not agree, a third determination was made and the two VFTs in closest agreement were averaged. If, after three determinations, two did not agree with 2 to 3 ma the experiment was not included in the series. One dog was excluded from the study because the fibrillation threshold was not reproducible within the limit of 3 ma.

The animals were then given either pronethalol\(^2\) or propranolol\(^3\) iv. Six preliminary experiments were performed using 2.0 mg/kg of pronethalol. This dose produced an average increase in VFT of 7 ma; however, the effects were quite variable (range of increase in the 6 dogs was 1 to 16 ma). A dose of 4 mg/kg of pronethalol was given to the dogs described in this report. Since propranolol is ten times more active than pronethalol as a beta-receptor antagonist (14), 0.4 mg/kg of propranolol was used. These doses, pronethalol 4.0 mg/kg and propranolol 0.4 mg/kg, are approximately twice the minimum doses required to block the chronotropic response to an intravenous injection of 10 \(\mu\)g of isoproterenol\(^4\) (15).

The VET and VFT were determined in duplicate or triplicate as indicated above, 15 min after the administration of the beta-blocking agent. Five dogs were included in the propranolol series and seven in the propranolol series. Three of the seven dogs in the propranolol series were given an additional 3.6 mg/kg of propranolol period at intervals of 2 to 3 msec. The ECG was observed for the occurrence of single premature beats, multiple responses, or ventricular fibrillation. The amplitude of the test stimulus was increased in 5-ma steps, scanning the vulnerable period after each increase until ventricular fibrillation was obtained. The least amount of current required to induce fibrillation by a single pulse timed to occur during the vulnerable period was designated the ventricular fibrillation threshold (VFT). The hearts were defibrillated within 30 sec and 15 min were allowed to elapse for restoration of a steady state\(^1\). VET and VFT were then determined a second time. During the second determination the amplitude of the test pulse was increased by 2- to 3-ma steps through a range which encompassed the previously determined fibrillation threshold so that a more exact estimate of VFT could be made. In most instances, these two determinations agreed within 2 to 3 ma. If they did not agree, a third determination was made and the two VFTs in closest agreement were averaged. If, after three determinations, two did not agree with 2 to 3 ma the experiment was not included in the series. One dog was excluded from the study because the fibrillation threshold was not reproducible within the limit of 3 ma.

The animals were then given either pronethalol\(^2\) or propranolol\(^3\) iv. Six preliminary experiments were performed using 2.0 mg/kg of pronethalol. This dose produced an average increase in VFT of 7 ma; however, the effects were quite variable (range of increase in the 6 dogs was 1 to 16 ma). A dose of 4 mg/kg of pronethalol was given to the dogs described in this report. Since propranolol is ten times more active than pronethalol as a beta-receptor antagonist (14), 0.4 mg/kg of propranolol was used. These doses, pronethalol 4.0 mg/kg and propranolol 0.4 mg/kg, are approximately twice the minimum doses required to block the chronotropic response to an intravenous injection of 10 \(\mu\)g of isoproterenol\(^4\) (15).

The VET and VFT were determined in duplicate or triplicate as indicated above, 15 min after the administration of the beta-blocking agent. Five dogs were included in the propranolol series and seven in the propranolol series. Three of the seven dogs in the propranolol series were given an additional 3.6 mg/kg of propranolol period at intervals of 2 to 3 msec. The ECG was observed for the occurrence of single premature beats, multiple responses, or ventricular fibrillation. The amplitude of the test stimulus was increased in 5-ma steps, scanning the vulnerable period after each increase until ventricular fibrillation was obtained. The least amount of current required to induce fibrillation by a single pulse timed to occur during the vulnerable period was designated the ventricular fibrillation threshold (VFT). The hearts were defibrillated within 30 sec and 15 min were allowed to elapse for restoration of a steady state\(^1\). VET and VFT were then determined a second time. During the second determination the amplitude of the test pulse was increased by 2- to 3-ma steps through a range which encompassed the previously determined fibrillation threshold so that a more exact estimate of VFT could be made. In most instances, these two determinations agreed within 2 to 3 ma. If they did not agree, a third determination was made and the two VFTs in closest agreement were averaged. If, after three determinations, two did not agree with 2 to 3 ma the experiment was not included in the series. One dog was excluded from the study because the fibrillation threshold was not reproducible within the limit of 3 ma.

The animals were then given either pronethalol\(^2\) or propranolol\(^3\) iv. Six preliminary experiments were performed using 2.0 mg/kg of pronethalol. This dose produced an average increase in VFT of 7 ma; however, the effects were quite variable (range of increase in the 6 dogs was 1 to 16 ma). A dose of 4 mg/kg of pronethalol was given to the dogs described in this report. Since propranolol is ten times more active than pronethalol as a beta-receptor antagonist (14), 0.4 mg/kg of propranolol was used. These doses, pronethalol 4.0 mg/kg and propranolol 0.4 mg/kg, are approximately twice the minimum doses required to block the chronotropic response to an intravenous injection of 10 \(\mu\)g of isoproterenol\(^4\) (15).

The VET and VFT were determined in duplicate or triplicate as indicated above, 15 min after the administration of the beta-blocking agent. Five dogs were included in the propranolol series and seven in the propranolol series. Three of the seven dogs in the propranolol series were given an additional 3.6 mg/kg of propranolol

---

1. Surital,® Parke-Davis and Company, Detroit, Michigan.

2. Pronethalol,® ICI 38, 174, also known as Alderlin or Nethalide. Supplied by Ayerst Laboratories, New York, New York.

3. Propranolol,® ICI 45, 520, also known as Inderal. Supplied by Ayerst Laboratories, New York, New York.

VENTRICULAR FIBRILLATION THRESHOLDS

Results

Table 1 summarizes the results of these experiments. In dogs given 4.0 mg/kg pronethalol, VFT increased an average of 11 ma, or 45%, above control values. An increase of VFT failed to occur in only one dog after giving 4.0 mg/kg of pronethalol. In this dog the VFT increased 8 ma with the administration of an additional 2.0 mg/kg of pronethalol. Thus in all dogs, pronethalol in a dosage of 4 to 6 mg/kg produced a significant increase in the fibrillation threshold of the ventricle.

The number of experiments is insufficient to characterize the dose-response curve accurately for pronethalol. However, in our preliminary experiments 2.0 mg/kg of pronethalol produced an average increase in VFT of 7 ma, and in these experiments 4.0 mg/kg of pronethalol produced an average increase in VFT of 11 ma. Within the range of 0 to 4.0 mg/kg, the effect of pronethalol on VFT appears to be dependent on the dose administered.

In dogs given propranolol, 0.4 mg/kg, VFT increased an average of only 1 ma, a change which was not statistically significant. Three of these dogs were given additional propranolol so that a total dose of 4.0 mg/kg was administered. This was done to determine if a dose of propranolol equivalent by weight to that of pronethalol would have the same quinidine-like effect on VFT. No consistent results were obtained. VFT decreased slightly in 2 dogs and increased in 1 dog. The latter dog also was of interest because, although VFT increased after 4 mg/kg of propranolol, the multiple response threshold was not altered. A similar result was noted in 1 dog given 4 mg/kg of pronethalol; the VFT increased 90% but the multiple response threshold did not change.

The excitability threshold of the ventricle averaged 0.1 ma during control observations. No significant changes of VET were observed with pronethalol or propranolol.

Discussion

These data show clearly that pronethalol causes a significant increase in VFT, but propranolol causes little or no change when the drugs are given in doses that have equivalent activity as beta-receptor antagonists (14, 15). This finding suggests that the increase in VFT observed with pronethalol is not a consequence of its beta-blocking effect. Wallace et al. (15) have demonstrated in the normal awake dog that pronethalol slows conduction in Purkinje fibers and prolongs ventricular activation time and that propranolol produces none of these changes. Results similar to those noted above have been observed when pronethalol and propranolol were given to dogs with chronically denervated hearts (Wallace, A. G., unpublished data). The differences between the responses to pronethalol and propranolol, the failure of cardiac denervation to alter the response to pronethalol, and the similarity between the effects of pronethalol and those of quinidine (Wallace, A. G., unpublished data) suggest that pronethalol has an extra-adrenergic, quinidine-like effect on the heart. This view is supported by the work of Sekiya and Vaughn Williams (16) who found that pronethalol and quinidine have similar effects on the transmembrane action potential of atrial muscle, and by the work of Singer et al. (17) who showed that pronethalol has a quinidine-like effect on Purkinje fibers. Lucchesi (18) has presented further evidence that the antiarrhythmic properties of pronethalol are not related specifically to its action as a beta-receptor antagonist. He has shown that although the D-isomer of pronethalol is only one-fortieth as potent a beta-block-

---

**TABLE 1**

Effects of Beta Blockade on Ventricular Fibrillation Thresholds (VFT)

<table>
<thead>
<tr>
<th>VFT</th>
<th>Pronethalol, 4.0 mg/kg (5 dogs)</th>
<th>Propranolol, 0.4 mg/kg (7 dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (ma)</td>
<td>Mean and SE</td>
<td>Mean and SE</td>
</tr>
<tr>
<td>Change (ma)</td>
<td>+ 11 ± 5</td>
<td>+ 1 ± 4</td>
</tr>
<tr>
<td>Per cent change</td>
<td>+ 45</td>
<td>+ 5</td>
</tr>
<tr>
<td>P value of change</td>
<td>&lt; 0.05</td>
<td>&lt; 0.35</td>
</tr>
</tbody>
</table>

*Analyzed as paired data with each dog serving as its own control.
ing agent as the racemic mixture each of the two forms is equally effective in abolishing certain arrhythmias.

Although propranolol does not produce changes in VFT, heart rate, A-V conduction or ventricular activation time, it is an effective antiarrhythmic agent for the treatment of certain arrhythmias resulting from excessive sympathetic activity or an overdose of digitalis (9-11). It seems probable that propranolol given in therapeutic doses depresses ectopic pacemaker activity and that this effect is the major factor which accounts for its antiarrhythmic action. This view has been supported recently in studies that demonstrate that propranolol markedly inhibits intrinsic activity of ventricular pacemakers in dogs with chronic A-V block (Wallace, A. G., unpublished data).

Finally, it seems appropriate to consider the relevance of measurements of the fibrillation threshold to the general problem of cardiac arrhythmias. There appears to be a correlation between the effects of certain agents on the fibrillation threshold and their likelihood of having either a fibrillatory or an antifibrillatory influence, but the electrophysiologic basis for this correlation is poorly understood. When a single stimulus is applied to the ventricle during its "vulnerable" period, one or multiple responses originate from the vicinity of the stimulating electrode. These multiple responses sometimes degenerate into fibrillation, but this is not always the case. The onset of fibrillation is initiated by an extraneous impulse that, in contrast to the multiple responses, originates at a distance from the stimulating electrode (19). It seems most likely that the application of a strong test pulse during the vulnerable period induces a long-lasting excitatory state in the vicinity of the electrode, which is then a source of rapid and multiple responses. If this local excitatory state persists for sufficient time, and if the multiple beats accelerate beyond the ability of more distal tissue to respond in an organized manner, then fibrillation ensues (20). According to this view, a change in the fibrillation threshold might represent a change of either the amount of current required to produce a particular pattern of multiple responses, or a change in the pattern of multiple responses which is required to induce fibrillation, or both. It is not surprising, therefore, that the multiple response threshold and the fibrillation threshold may differ, and that on occasion, such as was observed in this study, the fibrillation threshold can increase as the result of an intervention without a parallel change of the multiple response threshold.

Acknowledgment

We wish to express our gratitude to Mr. James Manley, Mr. William Joyner, Mr. Hubert Barber, Mr. Philip Talbert and Miss Eleanor Timmerman for assisting in this study.

References

9. Somani, P., and Lum, B. K. B.: Inhibition of 

Circulation Research, Vol. XIX, October 1966
Failure of Beta-Adrenergic Blockade to Alter Ventricular Fibrillation Threshold in the Dog: Evidence for Extra-Adrenergic Effects of Pronethalol
ROBERT A. ROSATI, JAMES A. ALEXANDER, ANDREW G. WALLACE, WILL C. SEALY and W. GLENN YOUNG, Jr.

Circ Res. 1966;19:721-725
doi: 10.1161/01.RES.19.4.721
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/19/4/721

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

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

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