Termination of Ventricular Tachycardia by an Increase in Cardiac Vagal Drive

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SUMMARY Out of 12 patients in whom phenylephrine terminated ventricular tachycardia, four were selected for detailed studies of its mechanism of action. Pretreatment with edrophonium (15–20 mg, i.v.) decreased, while atropine (2.4 mg, i.v.) increased by at least a factor of two, the dose of phenylephrine required to break ventricular tachycardia. Carotid sinus massage following pretreatment with edrophonium in unusually high (15–20 mg, i.v.) doses broke ventricular tachycardia in all four patients. The evidence presented supports the assumption that a vagal mechanism caused both instances of termination. These findings significantly alter our interpretation of vagal interventions in the bedside clinical diagnosis of wide QRS complex tachycardias.

VENTRICULAR TACHYCARDIA (VT) is believed to be unresponsive to enhanced vagal traffic, while supraventricular tachycardias are slowed or converted to normal rhythm. This time-honored method of clinical differentiation of supraventricular tachycardia with aberrant conduction and VT has become the subject of renewed interest. Recently, we reported that phenylephrine terminated six cases of ventricular tachycardia (VT). A considerable amount of attention was directed at trying to relate those terminations to a vagal mechanism, but we could not make a firm conclusion on the evidence we had. Since that report, we have examined 12 cases of VT which could be terminated by phenylephrine. Our observations in four of these cases aimed at elucidating the mechanism of phenylephrine’s action are detailed in this report.

Materials and Methods

Thirteen patients with VT were selected for challenge with phenylephrine based on the following criteria: 1) The VT was recurrent over five or more years. 2) The VT did not occur as a result of or in the presence of acute myocardial ischemia, acute myocardial infarction or severe left ventricular dysfunction of any etiology. 3) The VT produced minimal or no discernible adverse hemodynamic effects. 4) Pressor challenges with phenylephrine were deemed to be safe. In 12 of these 13 patients, phenylephrine terminated VT and among these, four were selected for very detailed examination of a possible vagal role in these terminations. The sole reason for selecting these four particular cases is that they had had numerous episodes of stable VT. In any one case comparisons could be made with either multiple spontaneously occurring episodes of VT or episodes induced by exercise, rapid right atrial or ventricular pacing or timed premature ventricular beats. Intracardiac electrograms were recorded with standard techniques and recorded on an Electronics for Medicine DR-12 recorder. Intracardiac stimulation was performed by means of a Grass S-88 stimulator coupled through stimulus isolation units. The drugs used in these studies included edrophonium hydrochloride (10–20 mg, i.v.), phenylephrine (0.1–3.0 mg, i.v.), atropine sulfate (1.8–2.4 mg, i.v.), isoproterenol (1–10 µg, i.v.) and propranolol (5 mg, i.v.).

The protocol for study was as follows:

A) The precise dose of phenylephrine needed to break two consecutive episodes of VT was determined. This was done by intravenous bolus injections of phenylephrine starting at a dose of 0.1 mg and increasing this in steps of 0.1–0.2 mg. The blood pressure was carefully monitored either continuously through an intra-arterial line or by repeated cuff determinations. An interval of at least five minutes following the return of the blood pressure to control was allowed to elapse between successive challenges.

B) During a third episode of VT, carotid sinus massage (CSM) was applied before and after pretreatment with 10, 15 or 20 mg edrophonium HCl. In instances where edrophonium was administered, right or left sided carotid sinus massage (CSM) was applied as soon as the patient felt some of the muscarinic side effects (about 30–40 seconds later).

C) During a fourth episode of VT (at least 30 min following step B), the patients were pretreated with a second dose of edrophonium identical to that which permitted VT termination in conjunction with CSM. The dose of phenylephrine needed to terminate VT was now reetermined by bolus injections similar to those used in (A).

D) During a fifth episode of VT (at least 30 minutes following step C), the patients were pretreated with atropine 2.4 mg, i.v. Conversion of VT with phenylephrine was now attempted using bolus injections starting at a dose of 0.5 mg and increasing this in steps of 0.2 mg. The maximum challenging dose was limited by not allowing the peak systolic pressure to exceed 200 mm Hg.

The nature and purpose of these studies was fully explained and informed verbal and written consent was obtained from each patient.

Results

Criteria for Ventricular Tachycardia

In all cases the diagnosis of VT was established by the following criteria: 1) The QRS complexes during the tachycardia were 120 msec or greater in duration and totally different from the complexes during supraventricular rhythm (figs. 1–9). 2) Atrioventricular (A-V) dissociation (figs. 1–3, 6, 8) or V-A block (fig. 7) was present. 3) Intermittent fusion and normal capture beats occurred (figs. 1, 2, 4). 4) Atrial pacing to rates in excess of the tachycardia did not produce aberration (fig. 2). 5) There was no His bundle potential preceding ventricular activation during the tachycardia. A His bundle potential preceded each QRS complex with a normal H-V interval when sinus rhythm was
restored. This was recorded without moving the catheter from its location during the tachycardia (figs. 3, 6, 8).

Dose Response of VT to Phenylephrine before and after Edrophonium

Pretreatment with edrophonium HCl reduced by at least a factor of 2 the dose of phenylephrine required to terminate VT in all four patients with correspondingly lower blood pressures at the time of the break (table 1, column B). In one of the patients (T.B.), five times less phenylephrine was required. Figures 4 and 5 illustrate this finding in patient T.B. During control conditions (fig. 4), a phenylephrine dose of 1.0 mg and a pressor response of 185/95 mm Hg were needed to terminate VT. The VT rate slowed from 180 to 150 beats/min with increasing doses of phenylephrine. Following pretreatment with 20 mg edrophonium (fig. 5), doses of phenylephrine as low as 0.2 mg and a pressor response of 150/85 mm Hg caused at least temporary conversion of VT. In this case, permanent conversion occurred at a dose of 0.4 mg phenylephrine. This contrasts sharply with the dose of 1.0 mg of phenylephrine needed to terminate VT during control conditions.

FIGURE 1. Patient M.W. Simultaneous recordings of leads I and II. The top panel shows the onset of VT. During the initial stages of VT there is A-V dissociation and frequent fusion beats (see arrows) occur. The bottom panel shows stable VT without any fusion beats.

FIGURE 2. Patient T.B. Continuous recordings of lead I (L1) and bipolar atrial electrogram (BAE) during VT. A-V dissociation is present during VT. The patient was pretreated with atropine to facilitate antegrade A-V conduction. Rapid atrial pacing is instituted as indicated between the arrows. As the atria gain partial capture of the ventricles, three fusion beats are generated prior to complete capture of the ventricles by the atria and normalization of the QRS complexes. Following cessation of pacing, VT resumes. The horizontal calibration line at the bottom represents one second.

FIGURE 3. Patient M.O. Simultaneous recordings of leads I, II, III and His bundle electrogram during VT. The tracing was taken 100 sec following an i.v. bolus of 1.0 mg phenylephrine and it shows reversion of VT back to atrial fibrillation. Note a clear H potential (see arrow) preceding each QRS during atrial fibrillation, but no H potential is seen during VT. These tracings were retouched.

FIGURE 4. Patient T.B. Recordings of lead I during VT at 25 mm/sec. The strips are not continuous. The second, third, and fourth strips show the peak response of 0.2, 0.5 and 1.0 mg phenylephrine respectively. Note that VT progressively slows from a control rate of 180 beats/min to 150 beats/min with phenylephrine. The bottom strip shows successful conversion to sinus rhythm. A single premature ventricular beat during sinus rhythm has a morphology identical to that of the VT.
Dose Response of VT to Phenylephrine Before and After Atropine

Following pretreatment with atropine, VT in all four patients was resistant to conversion by phenylephrine at twice the dose required for conversion under control conditions (table 1, column C). In patients J.Y. and T.B., VT during control conditions consistently broke following 0.4 mg and 1.0 mg phenylephrine respectively. Following atropine pretreatment, VT accelerated above the control rate and failed to revert after 1.0 and 2.0 mg phenylephrine respectively. Higher doses were not attempted because of the high blood pressure response at these doses. However, even in these instances, phenylephrine slowed the VT rate which had accelerated following atropine pretreatment (fig. 6).

Response of VT to CSM Plus Edrophonium

Carotid sinus massage alone did not break VT in any of the patients. The effect of right or left CSM following pretreatment with 10, 15 and 20 mg edrophonium was studied. Carotid sinus massage broke VT following 15 mg edrophonium in J.Y. and M.W. and 20 mg in T.B. and M.O. (table 1, column D). Figure 7 illustrates termination of VT by CSM in patient J.Y. following pretreatment with 15 mg edrophonium. Figures 8 and 9 (panel C) illustrate episodes of VT being terminated by CSM following pretreatment with 20 mg edrophonium in patient T.B. In figure 8 there is A-V dissociation during VT. Carotid sinus massage slowed the VT and independent atrial activity. Following restoration of sinus rhythm, a His potential not apparent during the VT now precedes the QRS without catheter repositioning.

Response of VT to CSM plus Propranolol

In two of the patients (T.B. and M.W.), the effect of CSM on VT following pretreatment with propranolol was studied. Propranolol was administered in successive i.v. boluses of propranolol 1 mg to a total dose of 5 mg which slowed but did not terminate the VT process. Following propranolol

<table>
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<tr>
<th>Pt/Age/Sex</th>
<th>Cardiac status</th>
<th>A. Phenylephrine</th>
<th>B. Phenylephrine</th>
<th>C. Phenylephrine</th>
<th>D. Edrophonium HCl with CSM</th>
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<tr>
<td>J.Y./32/F</td>
<td>normal</td>
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<tr>
<td></td>
<td></td>
<td>(180/95)</td>
<td>(150/85)</td>
<td>(195/100)</td>
<td>(110/75)</td>
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<tr>
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<td>0.5</td>
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<td>(125/90)</td>
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</table>

*Blood pressure at time of VT termination is indicated by figures in brackets under each corresponding drug dose.
†Amount of edrophonium HCl corresponds to the amount shown in column D.
‡Abbreviations: DMI = diaphragmatic myocardial infarction; CSM = carotid sinus massage; LV = left ventricular.
pretreatment right and left CSM consistently broke multiple episodes of VT (fig. 9, panel D). Following reversion to sinus rhythm, the adequacy of beta blockade was confirmed by observing no sinus acceleration following a challenging dose of isoproterenol (5 μg, i.v.).

**Discussion**

In view of the potential implications of these findings, it is crucial to be certain that the terminations of VT were not spontaneous but were indeed a direct result of the interventions used. Our claim that these terminations were not spurious spontaneous breaks is based on the following. First, episodes of VT were stable, lasting for many hours without interruption when left alone. Second, when spontaneous termination of VT took place, it was abrupt and there was no antecedent slowing of the VT rate, whereas slowing of VT rate occurred prior to most induced interruptions. Third, the interventions used terminated VT within seconds and the

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**Figure 6.** Patient T.B. Top panel records simultaneous lead I (L.), His bundle electrogram (HBE), and aortic blood pressure (BP) during an episode of VT. The dissociated atrial activity seen in the HBE is denoted by the arrows. Forty seconds after 1 mg phenylephrine, the independent VT and atrial rates which were 180 and 110 beats per minute respectively have slowed to 160 and 60 beats per minute. Conversion to sinus rhythm occurs and a clear H potential precedes the sinus propagated beats. No H potential is seen during VT. The bottom panel is recorded during a second episode of VT following pretreatment with atropine. A bipolar atrial electrogram (BAE) has been added. The arrows point to the dissociated atrial activity in the BAE. Following atropine, the VT has accelerated to 230 beats per minute, while the independent atrial activity has accelerated to 155 beats per minute. Despite 2 mg of phenylephrine and a higher pressor response, VT fails to terminate although the VT rate and atrial rate slow to 180 and 150 beats per minute respectively.

**Figure 7.** Patient J.Y. Simultaneous recordings of lead II and a bipolar atrial electrogram (BAE) during VT. In the top panel there is 1:1 V-A association. Forty seconds following 15 mg edrophonium (bottom panel) variable degrees of V-A block develop and finally carotid sinus massage (CSM) restores sinus rhythm. The morphology of two premature ventricular beats following return of sinus rhythm resemble the VT.
moment of termination corresponded well with the known onset of action of the maneuver used. Termination by the methods used was consistently reproducible in all instances.

The present study was designed to elucidate the mechanisms by which phenylephrine terminates some forms of VT. Although a cholinergic mode of action was strongly suspected, it had not been proven. The present demonstration that edrophonium potentiates and atropine reduced or prevented the capacity of phenylephrine to break VT provides evidence that a cholinergic mechanism is at least in part responsible for this action of phenylephrine. However, these observations do not permit conclusions regarding other possible concomitant modes of action such as a) reflex withdrawal of sympathetic drive, b) direct membrane effect, and c) myocardial stretch by the pressure response. It is entirely possible that other types of ventricular arrhythmias may respond predominantly through phenylephrine's other myocardial effects. Verrier et al. have shown that the ability of phenylephrine to raise ventricular fibrillatory threshold in the intact dog is mediated by a reduction in sympathetic drive and not by enhanced vagal drive.

The response of the VT process to CSM provides some sensitive insights into the interplay between the parasympathetic and sympathetic systems. Like phenylephrine, CSM has vagotonic and sympatholytic effects. Carotid sinus massage by itself did not interrupt VT. However, CSM could terminate VT provided that either vagal tone was...
enhanced by edrophonium pretreatment or sympathetic tone was antagonized by propranolol pretreatment.

Inasmuch as both phenylephrine and CSM share vagotonic and sympatholytic properties, the relative importance of the two effects in the termination of VT remains unresolved by our observations. It appears, however, that the two mechanisms may in fact be additive in the sense that an increase in the intensity of either may dampen the requirement for the other and it remains to be determined whether a strong enough pure vagal stimulus will by itself break VT at any level of sympathetic tone. A similar electrophysiologic interplay between vagal and sympathetic influences has recently been shown by Kolman et al. Using intact dogs, they showed that vagal stimulation could restore to normal the ventricular fibrillatory threshold which had been lowered by prior sympathetic nerve stimulation.

There is mounting evidence from different sources which suggests that the vagus nerve may modulate the electrical properties of ventricular tissues. Dressel and Sutter have shown that stimulation of the distal cut vagus nerve in dogs can abolish premature ventricular beats which are induced by cyclopropane-epinephrine mixtures. Bailey et al. demonstrated that automaticity in His bundle and proximal bundle branch cells is depressed by acetylcholine. Spear and Moore have shown that the ventricular pacemaker rate in experimentally induced heart block may be reduced by vagal stimulation. Kent et al. have shown that cholinergic influences raise the ventricular fibrillation threshold in dogs with experimental myocardial infarction while anti-cholinergic interventions reduce ventricular fibrillation threshold.

In addition, since several groups of investigators have identified histologically the presence of vagal nerve fibers within the ventricular septum of dogs, cats and man, it is conceivable that any vagaly sensitive VT process may involve this region in a crucial way.

It is not possible from our limited experience to date to speculate how frequently or what type of VT is likely to terminate with the maneuvers herein described. The constraints imposed by our selection criteria limited our observations to what may be a homogeneous group of "idiopathic" recurrent VT. Because of the acute rises in blood pressure which result from phenylephrine administration, this form of testing or treatment will have to be used with great discretion in the more common cases of VT which occur in the settings of coronary artery disease or left ventricular dysfunc tion of diverse causes. It is of interest that all four cases of VT were easily started by exercise and the maneuvers successfully used to convert VT in these patients would tend to counter the autonomic effects of exercise. It is thus possible that the relative balance between vagotonic and sympatholytic requirements for conversion of a given VT may parallel the balance between vagolytic and sympathetic influences incurred during its induction. This possible relationship requires further investigation.

Termination of VT by vagal maneuvers has not to date been a clinically recognized entity. In view of the frequency with which vagal maneuvers are used in the clinical diagnosis of tachyarrhythmias, the elusiveness of the described findings is notable. This could be explained in two ways. First, since it is widely accepted that a wide QRS complex tachycardia which breaks or slows with vagal maneuvers is of supraventricular origin, it is likely that at least some episodes of VT might have been erroneously labelled to be supraventricular purely on the basis of their response to vagal maneuvers. Second, it appears that the degree of cardiac vagal drive required to end VT in our cases may be very considerable. This is reflected in the high doses of anticholinesterase employed in tandem with CSM as well as the high vagal potency of the pressor agent used. In fact, our failure to break VT with CSM in conjunction with edrophonium in our previously described cases of phenylephrine terminated VT seems to have been related to the use of inadequate doses of edrophonium. This occurred despite the use of doses (10 mg) which provided a clear vagal endpoint in the form of selective slowing of the atrial rate. This underscores the fact that enhanced vagal drive sufficient to affect supraventricular structures may not be adequate to also influence ventricular tissue.

Our findings should in no way be construed as undermining the general usefulness of vagal interventions in the clinical differentiation of wide QRS complex tachycardias. However, when unusually potent vagal stimuli are required to break a wide QRS complex tachycardic process, the clinician should be alerted to the possibility of VT. Furthermore, in attempting to break VT with phenylephrine, the concomitant use of edrophonium should increase both the success rate and safety in terms of the maximal pressor response required.

References
A Study of the Human Heart as a Multiple Dipole Source

IV. Left Ventricular Hypertrophy in the Presence of Right Bundle Branch Block

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AND JOHN O. KRAMER, JR., M.S.

SUMMARY This report concerns the task of electrocardiographic (ECG) diagnosis and quantitation of left ventricular hypertrophy (LVH) in patients with right bundle branch block (RBBB). In 36 patients with RBBB the left ventricular mass (LVM) of each patient was independently known from quantitative biplane angiography. Two ECG techniques, standard 12-lead ECG and multiple dipole electrocardiography (MDECG), were evaluated. In diagnosing LVH, the best performance of the several standard ECG criteria was sensitivity = 29%, specificity = 100%, and that of the MDECG was sensitivity = 94%, specificity = 96%. In quantitating LVH, the standard ECG gave a correlation with LVM of r = 46% and a standard error of estimate of 98 g. The corresponding figures for the MDECG were r = 81% and the root mean square prediction error = 64 g.

These results confirm other studies showing that the conventional ECG is of only marginal value in the task of diagnosing LVH in the presence of RBBB. In contrast, the MDECG performs well both in this task and that of quantitating LVH. The results provide further support of the accuracy of the model of the cardiac electrical generator and volume conductor used in the MDECG method.

THE PRESENT REPORT deals with the continuing assessment of an advanced electrocardiographic (ECG) method referred to as multiple dipole ECG (MDECG). In 1969 the present authors published a report on the MDECG and its ability to detect and quantitate LVH. The results were established using a series of 72 patients with normal conduction. A strong correlation (predicted theoretically) was demonstrated experimentally between the dipole activity in the left ventricle and septal segments, which is a quantity derived from MDECG, and the left ventricular mass (LVM) derived from quantitative biplane angiography. The regression equation obtained from the correlation can now be used to predict LVM on the basis of MDECG measurements. A prospective study using a new series of 113 patients with normal conduction has proved that the prediction has a root mean square error of 66 g in such patients.

The effectiveness of an ECG technique for determining the presence or absence of some particular cardiac condition, or combination of conditions, may be studied by trials on a series of patients. This series must be composed of patients for whom the presence or absence of the conditions is independently and reliably known. Only then can the accuracy of the ECG predictions be assessed.

The present paper reports results on a series of patients with right bundle branch block (RBBB) and compares the ability of the standard 12-lead ECG and the MDECG to detect and quantify LVH in this situation. In addition, this study provides further validation of the modeling assumptions used in the MDECG method. The non-ECG method used to determine the presence and degree of LVH was quantitative biplane angiography.

Materials and Methods

To date, 126-lead ECG data have been recorded on 1,234 patients and normal subjects, as part of the MDECG
Termination of ventricular tachycardia by an increase in cardiac vagal drive.
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