Phenylephrine (Neo-synephrine) Terminated Ventricular Tachycardia


SUMMARY
Five cases of recurrent, wide QRS complex tachycardia which could be terminated with phenylephrine are presented. These cases fulfilled all accepted criteria for ventricular tachycardia. Carotid sinus massage with and without edrophonium hydrochloride had no effect on the ventricular activity but selectively slowed the atrial rate in cases of atrioventricular (A-V) dissociation, or blocked retrograde conduction in cases of A-V association. The mechanism of action of phenylephrine remains unclear.

These cases have many possible implications. Two of the most important are: 1) phenylephrine may be useful in terminating certain cases of ventricular tachycardia; 2) termination of an unknown, regular, wide QRS complex tachycardia by phenylephrine, and possibly other pressors, can no longer be taken as proof of a supraventricular mechanism.

Additional Indexing Words:
Atropine
His bundle electrograms
Valsalva maneuver

Carotid sinus massage
Lidocaine
Edrophonium
Phentolamine

WHEN ONE IS CONFRONTED by a regular tachycardia with a wide or abnormal QRS morphology, one must differentiate between a supraventricular tachycardia (SVT) with aberrant conduction and ventricular tachycardia (VT).1 2 One of the most useful and frequently employed techniques in making this distinction is to observe the response of the tachycardia to an induced increase in cardiac vagal drive.3 This is generally accomplished by carotid sinus massage with or without the addition of a cholinesterase inhibitor-edrophonium hydrochloride.4 5 It is generally accepted that an increase in cardiac vagal activity will terminate or slow a supraventricular tachycardia, but will have no effect on the ventricular rate in ventricular tachycardia.5 6 7 When carotid sinus massage, used in combination with edrophonium hydrochloride, fails to alter a tachycardia, and a SVT is still suspected, the clinician often tends to attempt to increase cardiac vagal drive by means of a pressor agent such as phenylephrine.8 9

We recently encountered a young man with recurrent tachycardias. The diagnosis of paroxysmal atrial tachycardia with aberrant conduction was based on the prompt conversion of the arrhythmia to normal sinus rhythm following an i.v. bolus injection of phenylephrine (fig. 1). However, careful analysis of this case proved that this was in fact a case of VT. Stimulated by this experience, we have attempted to convert VT with this drug in four other individuals. The present report deals with five consecutive patients in whom ventricular tachycardia was successfully terminated with phenylephrine.

Materials and Methods
Five patients with well-documented repetitive tachycardias form the basis of this report. The cases all have a number of important points in common: 1) the attacks were recurrent; 2) the morphology of each tachycardia was always the same; 3) the attacks never showed any signs of spontaneous termination; 4) all had a normal blood pressure (range 110-140/70-90 mm Hg) and were free of congestive heart failure or angina during the tachycardia. Table 1 outlines the major features of these cases. Only one of the patients had significant cardiac disease. All of the patients were assessed on at least one occasion when they were receiving no medication. The tachycardia could be induced by exercise in all and by right atrial pacing in two. This allowed for detailed and repetitive studies in these patients. In three of the patients (A.N., M.O., T.B.) a given episode of VT could be permanently converted to sinus rhythm. In the other two (M.B. and D.S.) the VT break was transient, lasting up to 10 sec.

Intracardiac recordings were performed by standard techniques and recorded on an Electronics for Medicine DR-12 recorder.10 Intracardiac stimulation was performed by means of a Grass S-88 stimulator coupled through

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stimulus isolation units. The drugs used in these studies included phenylephrine (1–3 mg i.v.), atropine sulfate (2.4 mg i.v.), phentolamine (5 mg i.v.), edrophonium hydrochloride (10–15 mg i.v.) and lidocaine hydrochloride (100–300 mg i.v.). Informed consent was obtained from each patient.

Results

Criteria for Ventricular Tachycardia

In all five cases the diagnosis of VT was established by surface and intracardiac electrocardiographic criteria. Since the importance and uniqueness of these cases rests on the accuracy of the diagnosis of VT, we will present the criteria in detail from a single representative case (M.B.). Figure 2 shows the ECG during normal sinus rhythm. The frontal plane axis is −30° and the T waves are inverted in V1–V4. These abnormalities had been present without change since age 10. Figure 3 shows a typical episode of VT. The QRS morphology shows left bundle branch block (LBBB) pattern. The atria and ventricles are dissociated (see fig. 5). In figure 4, the atrial rate was increased by atropine. As the atrial rate approaches and then exceeds the VT rate, we see fusion beats and then normal capture beats. In figure 5 bipolar atrial and His bundle electrograms are recorded simultaneously with leads I, II, and III. A His bundle potential is not seen preceding the ventricular activity during VT, and the atria and ventricles are dissociated. Following conversion to sinus rhythm, a His bundle potential could be recorded without altering the catheter’s position.

Response to Carotid Sinus Massage

In all cases the effect of individually applied right and left carotid sinus massage (CSM) was assessed with and without edrophonium hydrochloride (Tensilon). This maneuver slowed the atrial rate in those in whom there was A-V dissociation, and it blocked

**Table 1**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Cardiac status</th>
<th>Cardiac catheterization</th>
<th>Ventricular tachycardia characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.N.</td>
<td>M</td>
<td>26</td>
<td>Normal</td>
<td>Normal hemodynamics.</td>
<td>Associated and dissociated LBBB</td>
</tr>
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<td></td>
<td></td>
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<td></td>
<td>Normal coronary angiograms</td>
<td></td>
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<tr>
<td>M.B.</td>
<td>M</td>
<td>20</td>
<td>Normal</td>
<td>Not done</td>
<td>Dissociated LBBB</td>
</tr>
<tr>
<td>M.O.</td>
<td>F</td>
<td>45</td>
<td>Aortic insufficiency and mitral stenosis. D.M.I. — remote</td>
<td>Normal coronary angiograms, Localized diaphragmatic akinesia. Moderate mitral stenosis. Moderate aortic insufficiency</td>
<td>Associated and dissociated LBBB</td>
</tr>
<tr>
<td>D.S.</td>
<td>M</td>
<td>26</td>
<td>Normal</td>
<td>Normal hemodynamics.</td>
<td>Associated and dissociated RBBB</td>
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<tr>
<td></td>
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<td>Normal coronary angiograms</td>
<td></td>
</tr>
<tr>
<td>T.B.</td>
<td>F</td>
<td>36</td>
<td>Aortic insufficiency</td>
<td>Trivial aortic insufficiency. Normal coronary angiograms</td>
<td>Dissociated LBBB</td>
</tr>
</tbody>
</table>

Abbreviations: A-V = atrioventricular; LBBB = left bundle branch block pattern; RBBB = right bundle branch block pattern; DMI = diaphragmatic myocardial infarction.

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retrograde conduction in those who were A-V associated. These responses indicated that CSM had in fact increased cardiac vagal activity. Carotid sinus massage had no effect on the ventricular rate in any of the cases. The response of patient A.N. is representative of the group. Figure 6 is a recording of lead III taken 30 sec following the intravenous administration of edrophonium hydrochloride (10 mg i.v.). It shows VT with 1:1 retrograde conduction. Following right CSM, 2:1 retrograde block ensues for the period of time indicated by the horizontal bar. During this period one sees the disappearance of P waves (seen as notches on the ST segments) in alternate beats.

Response to Valsalva Maneuver

Three patients (M.B, M.O, and D.S) had a history of episodes of tachycardia occasionally terminated with a Valsalva maneuver. In two cases (A.N. and M.B.) we could repetitively document transient terminations during or immediately following the strain phase of the Valsalva maneuver. Figure 7, taken from A.N., shows transient termination of VT during two separate Valsalva maneuvers. Under control conditions (top panel), the VT is stopped transiently and the arrows point to ST segments lacking retrograde P waves. The bottom panel was recorded following atropine (2.4 mg i.v.); again a Valsalva maneuver
breaks the tachycardia. On this occasion retrograde block did not develop.

Response to Intravenous Lidocaine

At some stage, the response of the tachycardia to an intravenous bolus of lidocaine was examined in each of the patients. In only one of the cases (T.B.) was lidocaine occasionally effective in terminating the tachycardia. In the other four cases lidocaine in dosages up to 300 mg over a five minute period was ineffective.

Response to Phentolamine

In all five cases the ventricular tachycardia could be interrupted by an intravenous bolus of phentolamine (Neo-synephrine). Two of the cases (T.B. and M.O.) had repeated spontaneous or induced episodes which allowed for a number of different interventions aimed at elucidating the mode of phenylephrine’s action. Figure 8, taken from case T.B., shows that 35 sec after the administration of phenylephrine (1 mg i.v.), when the peak aortic pressure approaches 165 mm Hg, the VT reverts to normal sinus rhythm. There is a clear His bundle potential present during sinus rhythm, but none during the VT. Furthermore the arrows point to the dissociated atrial activity as seen in the His bundle electrogram during the VT.

In patient T.B., phentolamine (5 mg i.v.) was administered during an episode of VT to antagonize the pressor response to phenylephrine (fig. 9). Phenylephrine doses of 1 mg and 2 mg i.v. produced a minimal pressor response and failed to convert the VT (left-hand panel). When a dose of phentolamine (3 mg i.v.), large enough to competitively overcome the effects of phentolamine was given, conversion to sinus rhythm took place (right-hand panel). During another episode of VT patient T.B. was pretreated with atropine (2.4 mg i.v.) prior to the administration of phenylephrine (fig. 10). Atropine prevented interruption of the VT by phenylephrine despite a pressor response which was greater than levels achieved when conversion did occur.

Patient M.O. had repeated spontaneous attacks of VT which were always terminated by 1–2 mg doses of phenylephrine, at a pressor level of 140/95 mm Hg. On one occasion during an episode of VT she was pretreated with atropine (2.4 mg i.v.) prior to the administration of phenylephrine; 1 and 2 mg doses of phenylephrine failed to affect the VT. A dose of 3 mg phenylephrine and a pressor response of 160/110 mm Hg were required for conversion to atrial fibrillation (fig. 11).

Discussion

Termination and/or interruption of the tachycardias by phenylephrine in all cases and the Valsalva maneuver in two suggest that the tachycardias were supraventricular with aberrant conduction. The presence of normal capture beats, fusion beats, A-V dissociation (spontaneous or induced) and the absence of His potentials during the tachycardia and their
presence on conversion to normal sinus rhythm, suggest that these cases are in fact VT. An A-V junctional tachycardia with aberrant conduction could conceivably occur in the setting of A-V dissociation. Against this is the lack of a recordable His bundle potential during the tachycardia. Also the presence of fusion and normal capture beats is evidence countering such an interpretation.

An A-V junctional reciprocating tachycardia of the Wolff-Parkinson-White (WPW) syndrome is likewise most unlikely because of the presence of A-V dissociation. It is theoretically possible, although not reported, that reciprocation in WPW could occur in the face of A-V dissociation. To make this plausible, one has to postulate some form of intra-atrial dissociation so that the atrial island connecting the WPW tract to the ventricles is isolated from the rest of the atria. Furthermore there was never any evidence of pre-excitation recorded on surface electrocardiograms over many years of observation.

The transient termination of at least two of the cases by a Valsalva maneuver is most unexpected in VT. The Valsalva maneuver in the normal circulation produces complex alterations in cardiac sympathetic and vagal traffic, along with dimensional changes of the heart. In general, termination of a tachycardia by a Valsalva maneuver is taken to indicate that the arrhythmia is of supraventricular origin. Blood pressure or intrathoracic pressure was not monitored during the performance of the Valsalva maneuvers and therefore we cannot state absolutely whether the termination occurred during or just after release of the strain. Atropine pretreatment failed to abolish Valsalva induced breaks of the VT in patient A.N.
This suggests that variations in cardiac vagal drive were not responsible for these interruptions. Whether the Valsalva maneuver acted through a reflex change in sympathetic traffic or a dimensional change in the heart remains unclarified.

Why these cases of VT should be responsive to...
phenylephrine remains unclear. A simple vagal or cholinergic mechanism is unlikely because carotid sinus massage with Tensilon, sufficient to change V-A conduction or the independent atrial rate, did not affect the VT in any of the cases. However, atropine prevented the phenylephrine termination in patient T.B. This suggests a possible cholinergic mechanism. In order to reconcile these observations one would have to postulate a cholinergic response with phenylephrine either more intense or different than that with CSM.

In patient M.O., atropine pretreatment still permitted termination with phenylephrine but only with an increased dose and pressure level. This response suggested the possibility that phenylephrine termination of VT took place through a noncholinergic mechanism. However it is recognized that the vagolytic effects of atropine can be competitively overcome. Accordingly conversion with a large dose of phenylephrine is possibly consistent with the idea that a critical level of vagal drive was required to overcome the atropine blockade.

The evidence for cholinergic innervation of the ventricles stems from several different experimental observations. These include: 1) demonstration of cholinesterase and cholinergic fibers throughout the ventricles, 2) depression of automaticity of proximal bundle branch cells by acetylcholine; 3) depression of left ventricular contractility by vagal stimulation; 4) alteration in ventricular fibrillation threshold when vagal drive is varied in animals with experimental myocardial ischemia.

In considering noncholinergic mechanisms, a number of possibilities have to be considered. First, phenylephrine through its pressor action may produce stretch of the ventricular endocardium. Stretch of Purkinje fibers is known to induce loss of membrane potential and in this way alter conduction. If phenylephrine produced stretch within the zones strategic to the tachycardia, one could see how the tachycardia might be terminated.

Second, phenylephrine, by raising the blood pressure, might be expected to reduce cardiac sympathetic drive reflexly. If the arrhythmia depended on a critical level of sympathetic drive, it may then terminate when phenylephrine is given. There is a very large body of experimental and clinical evidence linking arrhythmias with sympathetic activity. The fact that these cases were all exercise inducible is in favor of the notion that a critical level of sympathetic tone was required to initiate and possibly maintain the tachycardias.

Third, phenylephrine may exert a direct membrane effect and in this way may alter electrophysiologic

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**Figure 10**

Case T.B. Simultaneous recording of lead I, His bundle electrogram (HBE), bipolar atrial electrogram (BAE), and aortic pressure (AO BP) during VT. The patient was pretreated with atropine (2.4 mg i.v.). Fifty seconds after phenylephrine (2 mg i.v.) there is a marked pressor response but no change in the VT. Time lines-1 second intervals.

**Figure 11**

Case M.O. Recording of V4, during an episode of VT. The patient was pretreated with atropine (2.4 mg i.v.). 130 seconds post phenylephrine (3 mg i.v.) the tachycardia reverts to atrial fibrillation. Recording speed 25 mm/sec.
properties of the tissues responsible for the VT. Recent in vitro studies indicate that phenylephrine can increase the refractory period of atrial and ventricular tissues in the guinea pig\(^{30}\) and rabbit\(^{31}\) as well as Purkinje cells of the sheep.\(^{32}\) This effect could be prevented by phentolamine. Additional in vitro studies indicate that another alpha agonist, methoxamine, can produce complete block in partially conducting Purkinje fibers.\(^{32}\) This effect could be at least partially reversed by an alpha-adrenergic blocking agent — phentolamine. In patient T.B. a higher dose of phenylephrine (3 mg i.v.) was required to terminate the VT in the presence of phentolamine. This could be equally consistent with phenylephrine exerting its effect directly on myocardial alpha-adrenergic receptors, as with an action secondary to its pressor effect.

Fourth, the pressor effect of phenylephrine may have altered patterns of regional coronary blood flow. Such an action could have secondary effects to increase or lessen local areas of myocardial ischemia. Such changes could in turn result in altered electrophysiologic properties in regions responsible for the tachycardia. One previous report of pressor-terminated VT proposed such a mechanism, operating in the setting of myocardial infarction and hypotension.\(^{34}\) In none of our cases was hypotension observed. In only one case (M.O.) was there any evidence of possible ischemic heart disease. That patient had sustained a diaphragmatic myocardial infarction, probably due to embolism secondary to her mitral valve disease since the coronary angiograms were normal.

**Conclusions**

Five cases of VT are presented in which termination could be produced by intravenous phenylephrine. The observations made are too few in number to offer any definite single mechanism for this action. Elucidation of this action could shed important light on the mechanisms underlying VT. Two major implications emerge: First, phenylephrine and related drugs may be useful in terminating certain cases of ventricular tachycardia. This is especially noteworthy since, in four of the five cases, lidocaine did not break the tachycardia. Second, termination of a wide QRS complex tachycardia of unknown origin by phenylephrine can no longer be taken as evidence proving a supraventricular mechanism.

**Addendum**

Since submission of this manuscript, we have terminated a sixth case (J.K.) of recurrent VT in a 20-year-old man who is free of any heart disease. Like the other patients, he was normotensive during the tachycardia. In this man, careful dose response observations were made. Boluses of phenylephrine were given in 0.1 mg increments from a minimal dose of 0.1 mg to a maximum of 1.0 mg i.v. A dose of 1.0 mg and a pressor level of 180/110 mm Hg was required to terminate the tachycardia. Lower doses had no effect on the tachycardia apart from slowing the independent atrial mechanism. (The patient was A-V dissociated during the tachycardia.)

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