Verapamil induced premature ventricular beats before reversion of supraventricular tachycardia

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The occurrence in 6 patients of premature ventricular beats before reversion to sinus rhythm, after the intravenous administration of verapamil—for the treatment of supraventricular tachycardia, is reported.

Four patients had pre-excitation syndromes (Wolff-Parkinson-White in 1 and Lown-Ganong-Levine in 3) and one patient had bradycardia-tachycardia syndrome. In the remaining patient, at previous studies, reciprocating tachycardia had been documented as the mechanism for recurrent supraventricular tachycardia. It is suggested that the supraventricular tachycardia in these 6 patients was probably caused by a reciprocating mechanism.

The patient with bradycardia-tachycardia syndrome developed ventricular tachycardia ('torsades de pointes'). In this and one other patient, the ventricular ectopics were probably responsible for termination of supraventricular tachycardia. The possible mechanisms for the occurrence of premature ventricular beats after verapamil in these patients are discussed.

Verapamil given by intravenous route has been reported to be effective in the treatment of supraventricular tachycardia. Though the exact mechanism of action is uncertain, prolongation of the atrioventricular nodal conduction appears to play an important role (Husaini *et al.*, 1973; Schamroth, Krikler, and Garrett, 1972). Singh and Vaughan Williams (1972) suggest that the antiarrhythmic effect of verapamil may be related to its action in blocking the movement of ionized calcium across the myocardial cell membrane and this property may constitute a new, fourth class antiarrhythmic action.

This paper describes the occurrence of premature ventricular beats associated with verapamil induced reversion to sinus rhythm in 7 episodes of supraventricular tachycardia in 6 patients. In 1 of these 6 patients short runs of ventricular tachycardia occurred after drug administration. It is suggested that the mechanism of supraventricular tachycardia in these patients was a reciprocating tachycardia and the drug-induced premature ventricular beats were probably responsible for the termination of arrhythmias in at least two instances. The possible mechanism of ventricular ectopics after verapamil, a phenomenon peculiar to reciprocating tachycardia, is discussed.

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Subjects, methods, and results

The 6 patients all had long histories of recurrent supraventricular tachycardia. The clinical details are summarized in the Table.

Of the 6 patients, 4 had pre-excitation syndromes. Case 1 had Wolff-Parkinson-White syndrome (WPW) type B, and 3 patients (Cases 2, 5, and 6) had Lown-Ganong-Levine (LGL) syndrome (Lown, Ganong, and Levine, 1952). Two patients (Cases 2 and 6) with LGL had previously been admitted with atrial flutter with 1:1 conduction and ventricular rates of 300 a minute. Intracardiac conduction studies carried out in these 2 patients, while in sinus rhythm, had shown an attenuated AH response to increasing atrial pacing rates, suggesting accelerated atrioventricular conduction (Mandel, Danzig, and Hayakawa, 1971). The technique and normal range for the various components of the intracardiac conduction have been reported previously (Hunt and Vohra, 1973; Hecht *et al.*, 1973). One patient (Case 2) was treated with verapamil on two separate occasions. Case 3 had a bradycardia-tachycardia syndrome (Short, 1954). This patient had normal atrioventricular conduction while in sinus rhythm, but the corrected sinus node recovery time (850 msec) was slightly prolonged (Narula, Samet, and Javier, 1972). A temporary pacemaker electrode had been placed in the right

TABLE Clinical details

Case No.	Age (yr)	Sex	History	Electrocardiogram during sinus rhythm	Other drug therapy at time of admission	Previous electrophysiological studies while in sinus rhythm
1	43	M	Paroxysmal supra-ventricular tachycardia for 10 yr	WPW type B	Methyldopa 750 mg/dy; one dose practolol 200 mg orally (before admission)	—
2	18	M	Paroxysmal supra-ventricular tachycardia since childhood; atrial flutter with ventricular rate of 300/min once	PR 0.10 sec; normal QRS configuration	Digoxin 0.50 mg and practolol 200 mg a day	AH interval 50 msec at atrial pacing rates 100 to 120 and 60 to 65 msec at 130 to 160/minute; HV interval 30 msec
3	66	F	Occasional episodes of supraventricular tachycardia for 30 yr; frequent episodes and attacks of dizziness for 3 mth; persistent sinus bradycardia 40 to 50/min for many years	PR 0.16 sec; sinus bradycardia 40 to 50/min with frequent supra-ventricular ectopics	None for one week	Corrected sinus node recovery time 850 msec; retrograde P waves following paced ventricular beats
4	47	F	Recurrent palpitations for 12 yr; frequent episodes of supraventricular tachycardia lasting for up to 48 hr during the last 4 mth	PR 0.16 sec; digitalis effect	Digoxin 0.50 mg and practolol 200 mg/day	Episodes of supraventricular tachycardia frequently precipitated and terminated by induced ventricular ectopic beats; retrograde excitation of atria demonstrated by simultaneous low and high right atrial electrograms during episodes
5	44	F	History of palpitations for 30 hr; last attack 12 mth ago	PR 0.10 sec; normal width QRS	Nil	—
6	16	F	History of palpitations since childhood; 3 hospital admissions for supra-ventricular tachycardia; atrial flutter with 1:1 conduction once	PR 0.10 sec; normal width QRS	Digoxin 0.5 mg and propranolol 120 mg/day	No increase in AH (50 msec) interval on atrial pacing from 74 to 126/min; HV interval 38 msec

ventricle, but she was not being paced when she developed supraventricular tachycardia. In Case 4, the mechanism of supraventricular tachycardia was diagnosed as a reciprocating tachycardia within the atrioventricular node on the basis of previous electrophysiological studies, during which supraventricular tachycardia was precipitated and terminated by induced premature ventricular beats (Durrer *et al.*, 1967).

Verapamil was administered by intravenous injection in increments of 1 mg per minute. The electrocardiogram was recorded continuously and

the blood pressure was measured every 30 seconds during the injection. The mean dose of verapamil required for reversion was 6.4 mg (range 2 to 10 mg). None of the patients was in cardiac failure and there were no adverse haemodynamic effects associated with verapamil administration.

Case 1: Fig. 1

The electrocardiogram before verapamil shows supra-ventricular tachycardia at a rate of 185/minute (strip 1). Immediately before reversion two premature ventricular beats are recorded (strip 2). The interval between the

FIG. 1 Case 1: Supraventricular tachycardia in a patient with WPW lead II before and after verapamil. See text for discussion.

last QRS of the supraventricular tachycardia and the first premature ventricular beat is 0.40 sec as compared to 0.32 sec between the QRS complexes during the tachycardia. Sinus rhythm is restored after a pause of 1 sec and the sinus beats show a typical WPW configuration.

Case 2: Fig. 2A

Supraventricular tachycardia at a rate of 240/min (strip 1) is noted before drug administration. Multiple premature ventricular beats occur before reversion to

sinus rhythm and show a slight variation in the QRS configuration. The interval between the last QRS of the supraventricular tachycardia and the first premature ventricular beat is 0.34 sec as compared to 0.30 sec during the tachycardia. A premature ventricular beat is noted in strip 3 after reversion to sinus rhythm.

Fig. 2B shows the response to verapamil on a second occasion in the same patient. The 8th complex in strip 2 is, probably, of junctional origin. The 9th and the 10th complexes differ from those during supraventricular tachycardia or sinus rhythm in that there is no initial q wave, and suggest that the ventricular activation in the initial part is different, but both middle and terminal vectors are identical to those during supraventricular tachycardia. These beats are, probably, ectopics arising close to the atrioventricular junction, possibly in the anomalous pathway and are followed by a premature ventricular beat. The next two complexes are, probably, fusion beats. A sinus P wave is noted before the last premature ventricular beat in strip 2. Even after return to sinus rhythm (strip 3), two salvos of premature ventricular beats are noted.

Case 3: Fig. 3

Strip 1 shows the electrocardiogram during supraventricular tachycardia. The first complex in strip 2 shows a narrow QRS and is the last complex of the supraventricular tachycardia, this is followed by two early premature ventricular beats and the 4th complex is again of supraventricular origin, which is followed by a run of ventricular tachycardia. The QRS complexes during ventricular tachycardia are variable in shape and amplitude and the rate exceeds 200 a minute. After this, the sinus P wave is seen for the first time before another run of ventricular tachycardia. Strip 3 shows two runs of ventricular tachycardia interspersed with supraventricular tachycardia complexes. The last beat in strip 3

FIG. 2 Case 2: A and B show leads I and III during two separate episodes of supraventricular tachycardia with ventricular rates of 240 and 215 a minute, respectively. See text for details.

FIG. 3 Case 3: Bradycardia-tachycardia syndrome, supraventricular tachycardia at a rate of 180 a minute before verapamil. Strips 2 to 5 are continuous. The spike after the QRS of the first complex in strip 4 is an artefact. See text for details.

is of sinus origin, and the first two complexes in strip 4 are of sinus origin (there is a technical artefact after the first QRS of the sinus beat in strip 4). Multiple premature ventricular beats are noted at this stage and the 4th premature ventricular beat restarts the supraventricular tachycardia. Strip 5, again, shows two premature ventricular beats preceding reversion of this episode of supraventricular tachycardia.

Case 4: Fig. 4

Strip 1 shows supraventricular tachycardia at a rate of 185 a minute. The 6th complex in strip 1 is, probably, a fusion beat as the QRS and T axes are different from the preceding complexes. This is followed by two more beats of supraventricular tachycardia. Multiple premature ventricular beats occur next. The interval between the last QRS of the supraventricular tachycardia and the first premature ventricular beat is 0.48 sec as compared to 0.40 sec between the QRS complexes during tachycardia. The last three premature ventricular beats show a different morphology and the 4th and 5th premature beats are, probably, escape beats. The 3rd complex in strip 3 is a fusion beat.

FIG. 4 Case 4: Supraventricular tachycardia at a rate of 150 a minute. See text for discussion.

Case 5: Fig. 5

Strip 1 shows supraventricular tachycardia at a rate of 170 a minute. The 10th and the 13th beats in the second strip are smaller and wider than the QRS complexes during supraventricular tachycardia; however, the T wave axis is in the same direction, suggesting fusion beats. The interval between the last QRS of the supraventricular tachycardia and the first fusion beat is the same as the RR interval during the tachycardia. The 12th and the 13th complexes are premature ventricular beats. Restoration to sinus rhythm is noted after a brief pause and sinus beats show a short PR interval. Two multi-

FIG. 5 Case 5: Verapamil for supraventricular tachycardia. Note the short PR interval in sinus beat. see text for the detailed description.

focal premature ventricular beats are noted in strip 3, even after reversion to sinus rhythm.

Case 6: Fig. 6

Strip 1 shows supraventricular tachycardia at a rate of 180 a minute. After 2 mg verapamil, strip 2 shows slight alternation of RR cycle lengths before the occurrence of premature ventricular beats. Three premature ventricular beats are noted and are followed by two supraventricular complexes and a salvo of premature ventricular beats. After this there is a brief pause and a P wave is seen preceding the next premature ventricular beat. The following two beats are sinus beats, though the QRS voltages show some variation. Another run of ventricular tachycardia is noted before the sinus rhythm is established.

Discussion

Of 6 patients described here, 4 had pre-excitation syndromes. One had WPW, while 3 had Lown-Ganong-Levine syndrome. In the majority of cases with pre-excitation, the mechanism of supraventricular tachycardia is a reciprocating rhythm, utilizing two pathways, one for anterograde and the other for retrograde conduction (Schamroth and Yoshonis, 1969).

One patient had bradycardia-tachycardia syndrome, and reciprocating tachycardias are also frequent in this condition (Easley and Goldstein, 1971). Initiation and termination of the tachycardia by an appropriately timed atrial or ventricular beat is considered to be a strong point in favour of a reciprocating mechanism (Barold *et al.*, 1969; Durrer *et al.*, 1967). In our patient with bradycardia-tachycardia syndrome, supraventricular tachycardia

was initiated and terminated by premature ventricular beats.

In Case 4, the initiation and termination of tachycardia by induced premature ventricular beats had been demonstrated previously. If, as seems likely, these 6 patients all had reciprocating tachycardia, then termination of the arrhythmia by verapamil induced premature ventricular beats might be easily explained on the basis of interruption of the junctional reciprocating pathway by retrograde penetration of the premature ventricular beat, thus breaking the re-entry cycle (Durrer *et al.*, 1967).

Certainly, in Cases 3 and 5, the premature ventricular beats occur before or at the time of expected arrival of the next supraventricular tachycardia complex and the interruption of the re-entry cycle seems very probable.

Case 3 shows short runs of a ventricular tachycardia which resembles that described as '*torsades de pointes*' (Slama *et al.*, 1973). This type of ventricular tachycardia, which borders on ventricular fibrillation, is characterized by irregularity of rate and QRS amplitude, the rate often exceeding 200 a minute. Paroxysms commonly last for 5 to 30 seconds and resolve spontaneously. This arrhythmia may occur in the setting of chronic bradycardia and potassium depletion or may occur in response to quinidine or procainamide. Bens *et al.* (1973) report 2 cases of '*torsades de pointes*' and attribute it to prolongation of QT interval caused by prenylamine ('quinidine-like effect'). It is of interest to note that prenylamine has a similar calcium antagonistic effect (Lindner, 1971) to verapamil.

In Cases 1, 2, 4, and 6, the interval between the

FIG. 6 Case 6: Strips 1 to 3 are continuous. Slight alternation of RR intervals is noted just before ventricular ectopics preceding reversion to sinus rhythm following 2 mg verapamil.

last complex of the arrhythmia and the first premature ventricular beat is longer than the interval between the QRS complexes during the arrhythmia. The reversion of supraventricular tachycardia in these 4 patients cannot be attributed to the verapamil induced ventricular ectopics. It is, however, possible that the arrhythmia was terminated by concealed ventricular ectopics. The junction between ventricular muscle and Purkinje fibres is reported to be particularly prone to unidirectional block caused by many conditions (low sodium, high potassium, quinidine, and hypoxia), and usually the block affects anterograde conduction, sparing, or minimally affecting, the retrograde conduction (Bigger, 1973). In the presence of orthograde block, the retrograde conduction has to proceed only up to atrioventricular node (NH region) to interrupt the reciprocating pathway and terminate the arrhythmia (Fig. 7). That such selective orthograde block can occur is supported by a report from Samet, Castillo, and Bernstein (1967), who demonstrated retrograde conduction to the atria by rapid ventricular pacing in patients with orthograde block.

Another possibility that deserves consideration is that concealed His bundle ectopics (Rosen, Rahimtoola, and Gunnar, 1970) were responsible for the termination of the arrhythmia in these patients. This suggestion is supported to some extent by the multifocal origin of the premature ventricular beats and the atrioventricular nodal ectopics in one patient. If the arrhythmia were terminated by concealed ventricular or His bundle ectopics, the first apparent premature ventricular beats, seen in the electrocardiograms here, were in fact, the second ectopic beats.

In Case 6 (Fig. 6) the ventricular ectopics are preceded by alternation of RR cycle lengths. The

subject of alternation of RR cycle lengths has been discussed in detail in previous publications (Spurrell, Krikler, and Sowton, 1973; Vohra *et al.*, 1974). Such alternation in reciprocating tachycardia has been attributed to the unmasking of an additional pathway for anterograde conduction due to a 2:1 block in the original anterograde pathway or a 3:2 Wenckebach block in the final pathway. It is thus possible that reversion to sinus rhythm was caused by the drug induced block in the additional anterograde pathway. However, in none of the 4 cases of alteration of cycle length following verapamil reported by us, did ventricular ectopics precede reversion to sinus rhythm.

The possibility that these premature ventricular beats were caused by an escape ventricular rhythm occurring after the termination of supraventricular tachycardia was also considered. However, such a rhythm is usually regular, of unifocal origin, and even with an accelerated idioventricular rhythm, the rate does not normally exceed 100 a minute (Rothfeld *et al.*, 1968). In our patients, salvos of premature ventricular beats had rates of between 150 and 200 a minute.

It is apparent that the premature ventricular beats are not supraventricular ectopics with aberrant conduction, as they are not consistently preceded by longer RR cycles (Moe and Mendez, 1971). Fusion beats are frequently noted and some premature ventricular beats show atrioventricular dissociation.

It is noteworthy that in Case 2, an identical response was noted on two different occasions. It is, therefore, suggested that the emergence of a ventricular extrasystolic pacemaker was related to the administration of verapamil. One possible explanation for these drug induced premature ventricular beats in these patients may be that the arrival of the supraventricular impulse at the semi-protected cell enhances the ectopic charge by 'electrotonic influence'. This enables the ectopic charge to reduce threshold quickly, and the action potential is, thereby, prematurely precipitated (Schamroth, 1966). The electrotonic influence is the property which is likely to have been accentuated by the drug. The mechanism of facilitation, itself, may be a Wedensky phenomenon (Wedensky, 1903), or it may be a sudden dissipation of a pre-existing exit block around an ectopic pacemaker caused by verapamil.

Alternatively, the drug, because of its effect on the calcium ion transfer across the cell membrane, may have caused an abrupt reduction in the resting potential/threshold potential difference, either by lowering threshold or by reducing the resting potential.

Verapamil does not affect the maximum rate of

FIG. 7 Interruption of the reciprocal pathway by a premature ventricular beat in the presence of orthograde block.

depolarization or the duration of action potential, and the antiarrhythmic property of the drug has been attributed to its action of blocking the movement of ionized calcium across the cell membrane. It is probable that the ventricular ectopics in these patients reflect the transient, abnormal, unstable state of calcium flux produced by verapamil.

The role of calcium in the genesis of cardiac arrhythmia is extremely complex and depends on the dosage and the species studied, administration of other compounds, and electrolyte status, in particular, the potassium concentration. Both hypocalcaemia and hypercalcaemia have been reported to produce ectopic rhythms (Scherf and Schott, 1973). Though an increase in calcium decreases the excitability and vice versa, in the presence of normal K^+ and Mg^{++} large changes in calcium concentration can occur before affecting the action potential of the Purkinje fibres. The effects of high Ca^{++} counteracts the effects of high K^+ and the reverse also applies (Zipes, 1973).

Under experimental conditions, a reduction in extracellular calcium concentration causes delayed repolarization and oscillatory changes in membrane potential (Hoffman and Suckling, 1956). It has been suggested that these changes may initiate ectopic beats (Hoffman and Cranefield, 1964). However, recent experimental studies in the genesis of ventricular fibrillation have shown the importance of 'slow response' or action potential of partially depolarized fibres, which depend on the smaller currents arising from permeation of calcium ions (Cranefield, 1973). Verapamil, by its action in blocking the calcium uptake, acts as a slow channel inhibiting agent (Zipes, Fischer, and Nicoll, 1973; Watanabe and Besch, 1973) and should provide protection against re-entrant ventricular arrhythmias.

Although primarily used for treatment of supraventricular tachycardia, verapamil has been reported to reduce the frequency of premature ventricular beats (Schamroth *et al.*, 1972). Under experimental conditions, verapamil also protects against catecholamine induced ventricular arrhythmias and fibrillation (Melville, Shister, and Huq, 1964; Hanna and Schmid, 1970; Kaumann and Aramendia, 1968). In the light of these reports, the occurrence of premature ventricular beats in the patients described here is a highly unusual response to verapamil.

The appearance of verapamil induced premature ventricular beats before termination of supraventricular beats appears to be peculiar to reciprocating tachycardia. We have noticed it only in the 6 patients reported here out of some 50 patients with supraventricular tachycardia treated with intravenous verapamil. Husaini *et al.* (1973), who studied

the effects of verapamil on intracardiac conduction in patients in sinus rhythm, also made no mention of ectopic activity after the drug administration.

A possible explanation for the occurrence of verapamil induced premature ventricular beats in reciprocating tachycardia may be the proximity of the ectopic pacemaker to the alternate circuit, so that the discharge from this focus can emerge in the relative refractory period of the intraventricular conduction system. Further studies using His bundle electrograms, either during spontaneous or induced reciprocating tachycardia and its treatment by intravenous verapamil, should throw more light on the exact origin of verapamil induced ectopic activity and its possible role in termination of the arrhythmia.

We have observed four types of response to the administration of verapamil in supraventricular tachycardia before reversion to sinus rhythm.

1. Abrupt termination of arrhythmia as with carotid sinus pressure.
2. Slight reduction in the ventricular rate caused by delayed AV conduction followed by a short pause before reversion to sinus rhythm – a common response to beta-adrenergic receptor blockers.
3. Alternation of RR cycle lengths before reversion to sinus rhythm, which is preceded by a shorter RR cycle length.
4. Occurrence of ventricular ectopics followed by a pause and return to sinus rhythm.

It is felt that the type 4 response is peculiar to reciprocating tachycardia and type 3 is a very strong point in favour of intranodal reciprocation.

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