Effects of Nicorandil, a Potassium Channel Opener, on Idiopathic Ventricular Tachycardia

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Objectives. We assessed the effects of the adenosine triphosphate (ATP)–sensitive potassium channel opener, nicorandil, on ATP- and verapamil-responsive ventricular tachycardias (VTs).

Background. Adenosine- or ATP-sensitive VTs are thought to be due to a nonreentrant mechanism, presumably delayed afterdepolarization. We suggest that this potassium channel opener may suppress ATP- and verapamil-sensitive VTs.

Methods. The subjects included 13 patients with idiopathic VTs, 7 of whom had sustained VT and 6 of whom had nonsustained VT. We evaluated the effects of ATP, nicorandil and verapamil on VTs.

Results. Sustained VT: Verapamil had preventive effects on seven VTs. Four VTs were terminated by ATP, and of these, nicorandil terminated two and prevented exercise-induced VT in the two others. Three ATP-insensitive VTs, which were determined to be due to a reentry by an electrophysiologic study, were not terminated by nicorandil. Nonsustained VT: All six VTs were inhibited by ATP, and five of these were suppressed by nicorandil. Verapamil inhibited four of the five VTs. QT intervals and the corrected QT intervals were significantly shortened by nicorandil.

Conclusions. Nicorandil suppresses ATP- and verapamil-responsive VTs. One of the mechanisms of suppression by nicorandil might be related to a reduction of calcium in the myocardium, because it reduces the action potential duration.

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on the basis of the VTs, we evaluated drug efficacy in 13 patients with VT. All patients underwent treadmill exercise testing using the conventional Bruce protocol.

**Drug Testing for Sustained VT**

*Electrophysiologic study.* Electrophysiologic study of the patients with VT included assessment of baseline conduction intervals and characteristics of sinus node function and atrioventricular node conduction in the anterograde and retrograde directions. In the absence of either spontaneous VT or VT initiation during atrial stimulation studies, VT induction was undertaken using one to three ventricular extrastimuli and ventricular burst pacing at the right ventricular (RV) apex and outflow tract. If VT was not induced, isoproterenol infusion (0.01 to 0.02 μg kg⁻¹ min⁻¹) was initiated and the protocol was repeated. If VT could be reproducibly induced, we assessed the efficacy of three drugs using the following procedure.

*Administration of drugs.* In all individuals any cardioactive drugs were discontinued for a period equal to at least five drug half-lives before beginning the studies, and the test drugs were then administered.

*Adenosine triphosphate.* Adenosine triphosphate was administered as bolus intravenous injections of increasing doses (0.2, 0.3 and 0.4 mg kg⁻¹) after VT had been sustained for at least 30 s. If the tachycardia did not terminate within 2 min of the initial dose (0.2 mg kg⁻¹), the dose was increased until it did, or until the maximal dose of 0.4 mg kg⁻¹. If the ATP injection terminated VT, the reproducibility of the effect was assessed by administration of the same ATP dose on a second occasion.

*Nicorandil.* The effect of nicorandil on VT was assessed after ATP testing. Nicorandil (12 to 18 mg) was administered intravenously over 3 min during VT.

*Verapamil.* On a separate day, or 40 min after nicorandil administration, 10 mg of verapamil was infused slowly over 3 min during VT. When possible, assessment of prevention of VT by verapamil was evaluated by repeating the extrastimulus or pacing induction procedure.

The agents were considered effective in patients with sustained VT when the tachycardia was terminated or suppressed. We considered as ATP sensitive one patient whose tachycardia was markedly slowed (cycle length prolonged by 15%) but not terminated by ATP.

**QT Intervals**

We investigated the changes in QT intervals and the corrected QT interval (QTc) before and after nicorandil administration in 12 patients in whom ECGs were recorded (paper speed 400 mm s⁻¹). QT intervals were measured at the recording site showing the longest QT interval by two physicians, and QTc intervals were calculated according to the Bazett formula (QTc/√RR).

**Measurement of Serum Concentration of Nicorandil**

The serum concentration of nicorandil was measured 5 min after the administration of 12 mg of nicorandil using high-performance liquid chromatography at Mitsubishi-yuka BCL Inc. (Tokyo, Japan).

**Statistical Analysis**

Results are expressed as the mean value ± SD. Repeated measures analysis of variance followed by the Scheffé F test were used to compare measurements made before and after serial drug administration.
**Table 1. Characteristics of Ventricular Tachycardia and Efficacy of Drugs**

|---------|-----------|--------|------------------|---------------------||---------|------|
| I.M.    | 15        | M      | LBBB, LIA        | +                   | +        | +                 | +             |
| S.T.    | 38        | F      | LBBB, RIA        | +                   | +        | +                 | +             |
| G.T.    | 30        | M      | RBBB, RIA        | +                   | +        | +                 | +             |
| T.S.    | 60        | M      | RBBB, LIA        | +                   | +        | +                 | +             |
| H.T.    | 27        | M      | RBBB, RSA        | -                   | -        | -                 | +             |
| M.Y.    | 33        | F      | RBBB, RSA        | +                   | -        | -                 | -             |
| H.I.T.  | 38        | M      | RBBB, RSA        | +                   | -        | -                 | -             |

**Non-sustained VT†**

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*Sustained VT: All of seven VTs (two LBBB, five RBBB pattern) had terminative or preventive effects of verapamil. Four VTs (two LBBB, two RBBB pattern) were terminated by ATP. Nicorandil also terminated two of the four VTs and prevented exercise-induced VT in the two remaining patients. Three ATP-insensitive VTs due to reentry were not terminated by nicorandil. †Nonsustained VT: Six VTs (all LBBB pattern) were inhibited by ATP and five of the six VTs were suppressed by nicorandil. Verapamil also suppressed four of the five VTs that were tested. ATP = adenosine triphosphate; F = female; LBBB = left bundle branch block pattern; LIA = left inferior axis; M = male; NA = (data) not available; RBBB = right bundle branch block pattern; RIA = right inferior axis; RSA = right superior axis; Sens. = sensitivity.

**Results**

**Sustained VT.** As shown in Table 1, nicorandil was effective in four of the seven patients with sustained VT, who were then classified as having nicorandil-sensitive sustained VT. Nicorandil-sensitive sustained VTs had either an inferior axis exhibiting left bundle branch block (LBBB) morphology (n = 2) or right bundle branch block (RBBB) morphology (n = 2). The origin of VTs with an LBBB pattern was located in the RV outflow tract, and that of VTs with an RBBB pattern was in the left ventricular (LV) base. Three of four VTs were induced by exercise testing. In the patient whose VT was not induced, VPCs were exacerbated by exercise testing. In addition, all VTs were induced by ventricular extrastimulation. Isoproterenol infusion induced spontaneous VT in one patient (T.S.) and facilitated the other three VTs. All four VTs did not show entrainment phenomenon by ventricular pacing from the RV apex, RV outflow tract or LV apex. Two VTs (patients I.M. and T.S.) were terminated by nicorandil (Fig. 1). In patient G.T., the VT was barely induced by exercise testing after nicorandil injection, and the VT did not last more than 30 s. Consequently, exercise tolerance was increased (before nicorandil 5.3 metabolic equivalents after nicorandil 8.2). In patient T.S. nicorandil suppressed the VT and VPCs induced by isoproterenol infusion. In four patients in whom tachycardia was suppressed by nicorandil, ATP stopped VT in three and remarkably slowed it in one. Verapamil suppressed VTs in all four patients.

In contrast, nicorandil was ineffective in three of the seven patients with sustained VT, who were then classified as having nicorandil-insensitive sustained VT. The morphology of the VTs was an RBBB pattern with a superior axis. Two of the three VTs were exacerbated with catecholamines. The VTs were induced by ventricular stimulation in the control state in patient H.T. and under isoproterenol infusion in patients M.Y. and H.I.T. These three VTs originated from the LV septum and exhibited entrainment phenomenon by pacing from the RV outflow tract. The VTs were terminated by RV stimulation. The VTs were not terminated by ATP. However, verapamil terminated the VTs in all nicorandil-insensitive sustained VTs.

**Non-sustained VT.** All six non-sustained VTs had an LBBB pattern and an inferior axis (Table 1). An electrophysiologic study was performed in all patients. A sustained VT could not be induced in any of them by ventricular extrastimulation. Isoproterenol infusion facilitated non-sustained VTs in five patients. The electrophysiologic study showed that six VTs arose from the RV outflow tract. All six non-sustained VTs were inhibited by ATP. Nicorandil suppressed five of the six VTs. Verapamil also suppressed four of the five VTs tested. A representative case with non-sustained VT that revealed an LBBB pattern and an inferior axis is shown in Figure 2. Figure 2, A shows non-sustained VTs that were observed 45 times in a 3-min period (150 per 10 min) in the control state. The non-sustained VT was suppressed from six times in 30 s before administration of ATP to once in 30 s after administration of ATP. Couplets and non-sustained VTs were suppressed from 13 times in 30 s before administration of ATP to five times in 30 s after administration of ATP (reduction rate 83% and 62%, respectively) (Fig. 2, C). The non-sustained VTs were suppressed after nicorandil administration, from 45 times in 3 min...
before administration to 17 times in the same period after
administration (before administration 150 times in 10 min;
after administration 60 times in 10 min; reduction rate 60%)
(Fig. 2, C). As shown in Figure 2, B, 40 min later nonsustained
VT returned to the control level, and the VTs were suppressed
from 83 to 6 times in a 5-min period after verapamil adminis-
tration (before nicorandil 166 in 10 min; after postadmin-
istration 12 times in 10 min; reduction rate 93%) (Fig. 2, C).
Figure 3 shows the efficacy of nicorandil and verapamil on
the arrhythmias in all patients with nonsustained VT. The top
panel illustrates a time course of couplets and nonsustained
VTs that were nicorandil sensitive. The arrhythmias were
reduced significantly by nicorandil (before nicorandil 141 ± 99
in 10 min; after nicorandil 34 ± 40 in 10 min; p < 0.05), and
then reappeared 30 min later (68 ± 62 in 10 min). The
arrhythmias were reduced again after verapamil (4 ± 4 in
10 min). As shown in Figure 3 (bottom panel), verapamil
suppressed >50% of the arrhythmias in four of four patients
with nicorandil-sensitive nonsustained VT who were tested.
One VT (patient H.T.) was not suppressed by nicorandil and
verapamil, although ATP suppressed it.

QT intervals. We investigated changes in ECG records of
QT intervals before and after nicorandil administration,
using a paper speed of 400 mms⁻¹. The results (Fig. 4) are
from 10 patients who underwent isoproterenol loading and two patients without isoproterenol. The open circles in Figure 4 represent eight patients with nicorandil-sensitive VT and the crosses represent four patients with nicorandil-insensitive VT. In all 12 patients the RR intervals did not change after nicorandil (control vs. nicorandil: 514 ± 71 vs. 522 ± 86 ms; p = NS), although both the QT and QTc intervals were significantly reduced, from 349 ± 45 to 333 ± 49 ms (p < 0.05) and from 487 ± 43 to 461 ± 49 (p < 0.01), respectively. A similar trend was also seen in the patients in whom nicorandil was effective (control vs. nicorandil: RR—515 ± 73 vs. 511 ± 67 ms, p = NS; QT—359 ± 50 vs. 339 ± 50 ms, p < 0.05; QTc—500 ± 46 vs. 474 ± 51, p < 0.05). However, no significant difference was seen in the three indexes in patients in whom nicorandil was not effective (control vs. nicorandil: RR—511 ± 76 vs. 545 ± 125 ms, p = NS; QT—328 ± 27 vs. 320 ± 52 ms, p = NS; QTc—460 ± 15 vs. 434 ± 38, p = NS).

Serum concentration of nicorandil. The serum concentration of nicorandil in six patients, three of whom had nicorandil-sensitive VTs and three of whom had nicorandil-insensitive VTs, were 282 ± 210 ng ml⁻¹. There was no difference in the serum concentrations between the nicorandil-sensitive and the nicorandil-insensitive groups (273 ± 244 vs. 291 ± 224 ng ml⁻¹, p = NS).

Discussion

The results of this study revealed that nicorandil suppresses certain idiopathic VTs.

Ventricular tachycardias. The characteristics of the nicorandil-sensitive sustained VTs were induction by exercise, spontaneous onset or facilitation during isoproterenol, absence of entrainment and suppression by ATP and verapamil. Previous studies have shown that adenosine- or ATP-sensitive VTs...
do not result from reentry, but are presumed to be due to delayed afterdepolarization (6–9). Adenosine antagonizes the effects of beta-adrenergic agonists in ventricular cells because it inhibits the activation of adenylate cyclase by binding to P1 purinergic receptors. This may inhibit calcium current and abolish triggered activity. Recent reports suggest that adenosine may increase ATP-regulated K⁺ current (10, 11). This may in turn result in a decrease in calcium current owing to a reduction of the APD and suppress triggered activity. Exogenous ATP immediately metabolizes to adenosine, so ATP works in the same way as adenosine. Besides this, it has been reported recently that ATP enhances IK conductance through the P₂ purinergic receptor in atrial cells, and a similar phenomenon is presumed to occur in ventricular cells (12). We therefore consider that these factors may be related to the effects of ATP. In this study nicorandil-sensitive VT was also inhibited by ATP and verapamil, and the other results revealed delayed afterdepolarization as the mechanism of nicorandil-sensitive VTs. Another experimental study reported that the potassium channel opener, pinacidil, reduces APD and suppresses delayed afterdepolarization caused by ouabain (3). We consider that nicorandil was effective in patients in a similar

Figure 3. The efficacy of nicorandil and verapamil on nonsustained VTs. (Top) Time course of couplets and nonsustained VTs in five patients who had nicorandil-sensitive nonsustained VT. The arrhythmias were reduced significantly by nicorandil (before nicorandil: 141 ± 99 in 10 min; after nicorandil: 54 ± 40 in 10 min; p < 0.05), and then reappeared 30 min later (68 ± 62 in 10 min). The arrhythmias were reduced again after verapamil (4 ± 4 in 10 min). (Bottom) Percentage of inhibition of the arrhythmias by drugs. Verapamil suppressed >50% of the arrhythmias in four of four patients with nicorandil-sensitive nonsustained VT who were tested. One VT (patient H.T.) was not suppressed by nicorandil and verapamil, although ATP suppressed it.

Figure 4. Effect of nicorandil on QT intervals. (Open circles) Eight patients with nicorandil-sensitive VT. (Crosses) Four patients with nicorandil-insensitive VT. In all 12 patients the RR intervals did not change after nicorandil (p = NS), although both the QT and QTc intervals were significantly reduced. A similar trend was also seen in the patients in whom nicorandil was effective (control vs. nicorandil: RR—515 ± 73 vs. 511 ± 67 ms, p = NS; QT—359 ± 50 vs. 339 ± 50 ms, p < 0.05; QTc—500 ± 46 vs. 474 ± 51, p < 0.05). However, no significant difference was seen in the three indexes in patients in whom nicorandil was not effective (control vs. nicorandil: RR—511 ± 76 vs. 545 ± 125 ms, p = NS; QT—328 ± 27 vs. 320 ± 52 ms, p = NS; QTc—460 ± 15 vs. 434 ± 38, p = NS).
manner. The fact that QT intervals were reduced in the patients supports this belief. In contrast, nicorandil-insensitive sustained VTs had ATP insensitivity and verapamil sensitivity. The mechanism of the VTs was suggested to be reentry because of the induction and termination by ventricular stimulation and the presence of the entrainment phenomenon. Nonsustained VTs showing an LBBB pattern with an inferior axis arise from the RV outflow tract. These arrhythmias have the same characteristics as ATP- or adenosine-sensitive sustained VTs, and the mechanisms of the arrhythmias are suggested to be triggered activity (9,13,14). In this study six nonsustained VTs also arose from the RV outflow tract, and all of them had ATP sensitivity.

Nicorandil sensitivity was also seen in all but one patient. The exception had ATP sensitivity, nicorandil insensitivity and verapamil insensitivity. This may be because ATP has multiple effects on cardiac cells, as compared with nicorandil and verapamil. Some clinical reports have revealed that nicorandil abolished early afterdepolarization in long QT syndrome. However, to our knowledge this is the first report of the effects of nicorandil on idiopathic VTs. Our clinical study suggests that nicorandil, in a manner similar to that of ATP, is helpful in determining the initiating factor of ventricular arrhythmia. Nicorandil is effective for a longer period, and determination of its effectiveness is easier than that of ATP.

References

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