Effects of Verapamil and Lidocaine on Two Components of the Re-entry Circuit of Verapamil-Sensitive Idiopathic Left Ventricular Tachycardia

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OBJECTIVES
We characterized pharmacologically the slow conduction zone of verapamil-sensitive idiopathic left ventricular tachycardia (ILVT) with regard to the late diastolic potential (LDP).

BACKGROUND
We showed that the slow conduction zone of ILVT could be divided into two components by LDP; that is, the distal component with a tachycardia-dependent conduction delay property and the proximal one without it.

METHODS
Electrophysiologic studies were performed in eight consecutive patients. The LDP was recorded during left ventricular (LV) mapping during ILVT. Entrainment was performed from the right ventricular outflow tract while recording LDP. The effects of lidocaine (1 mg/kg body weight) and verapamil (0.5 or 1.0 mg) were examined during entrainment.

RESULTS
The LDPs preceding the Purkinje potential (PP) were serially recorded from the upper third to the middle of the LV septum along the narrow longitudinal line. The ventricular tachycardia (VT) cycle length increased after lidocaine (p < 0.05), and further after verapamil (p < 0.05). The increments in the VT cycle length after administration of the drugs strongly correlated with those in LDP-PP (r > 0.9 for both drugs). The interval from the ventricular potential to LDP was unchanged after administration of the drugs. In one patient, verapamil terminated VT by local conduction block between LDP and PP. The LDP-PP measured during entrainment increased after lidocaine, and further after verapamil, whereas the interval from the stimulus to LDP remained unchanged.

CONCLUSIONS
The component distal to LDP is mainly calcium channel-dependent and partly depressed sodium channel-dependent. The proximal component is considered to be sodium channel-dependent (normal). (J Am Coll Cardiol 2001;37:1415–21) © 2001 by the American College of Cardiology

Verapamil-sensitive idiopathic left ventricular tachycardia (ILVT) constitutes a relatively small but distinct entity occurring in relatively young patients (1–9). It has been shown in most patients that the underlying mechanism of ILVT is re-entry with an excitable gap (3–7). With the use of the entrainment technique (10–12), we showed that a slow conduction zone with a conduction delay property in response to the increase in the pacing rate is present between the right ventricular outflow tract (RVOT) and the earliest ventricular activation site at the posteroapical left ventricular (LV) septum. In addition, we found that small doses of verapamil and lidocaine selectively suppress conduction through this slow conduction zone of ILVT (4,5,7).

Recently, we reported that a discrete late diastolic potential (LDP) preceding the Purkinje potential (PP) was recorded in the middle to upper third LV septum during ILVT, and the entire slow conduction zone could be divided into two components by LDP: one in the distal part to the LDP recording site, showing a conduction delay property (the distal component), and the other in the proximal part to the LDP recording site, showing no conduction delay property (the proximal component) (7). In the present study, we examined the responses of these two components to lidocaine (a sodium channel-blocking agent) and verapamil (a calcium channel-blocking agent) both during ventricular tachycardia (VT) and entrainment.

METHODS
Study patients. Eight consecutive patients (6 men and 2 women, 16 to 44 years old) with recurrent, sustained VT and with no underlying heart disease were studied. The electrocardiogram (ECG) recorded during VT exhibited a right bundle branch block configuration and a superior or left axis in all patients. Intravenous verapamil (5 to 10 mg) was demonstrated to be effective in terminating VT in all patients. Electrophysiologic study. Written, informed consent was obtained from all patients before the study. All antiarrhythmic drugs were discontinued for 5 half-lives of each drug before the study. Using standard techniques, two or three 6F quadripolar electrode catheters (Josephson, Bard Electrophysiology, Billerica, Massachusetts) were placed at the right ventricular (RV) apex, RVOT and/or His bundle region and were used for recording bipolar electrograms and pacing. A 7F deflectable quadripolar electrode catheter with a 2-mm interelectrode interval (Radii-T, Cardiac Pathways, Sunnyvale, California) (n = 8) or a 6F deflectable eight-
leads (I, II, III, aVF, V1 and V5) with the use of a polygraph.

600 Hz and recorded simultaneously with three or six ECG

electrograms were filtered between a bandpass of 50 and

electrograms from each electrode pair. All bipolar

ventricular activation site and to record LDP by recording

endocardial mapping during VT to identify the earliest

beats/min, another dose of 0.5 mg (total dose 1.0 mg) was

administered. The entrainment study was repeated in seven

of eight patients. In the remaining one patient, verapamil

(1.0 mg) resulted in VT termination, and the entrainment

study was not performed. Throughout the study, we held

the catheter carefully to avoid applying pressure at the tip of

the catheter.

Before and after injection of each antiarrhythmic agent,

the VT cycle length and the intervals from PP to the local

ventricular potential (VP) (PP-VP), from VP to LDP

(VP-LDP) and from LDP to PP (LDP-PP) were measured

during VT. Measurements of st-LDP, st-RVA and

LDP-PP during entrainment were repeated at every pacing

rate after each antiarrhythmic agent.

Data analysis. Continuous variables were expressed as the

mean value ± SD. Statistical analysis was done with

repeated measures one-way analysis of variance, in which the

F value was interpreted on the basis of Huynh-Feld

corrected p values. Subsequent multiple comparisons were

performed by using a Bonferroni-type multiple comparison

test for three or more variables. Correlations were tested by

the Pearson correlation coefficient. For the analysis of the

effect of verapamil on the relationship between LDP-PP

and pacing rate, we performed a multiple regression analysis

using a dummy variable to encode the treatment condition

within each patient, as well as dummy variables to encode

the eight different patients. A p value <0.05 was considered

statistically significant.

RESULTS

Sustained VT with a mean cycle length of 342.8 ± 49.3 ms

(rate 178.3 ± 26.1 beats/min) and with the same QRS

morphology as that of spontaneous VT was repeatedly

induced in all patients. Endocardial mapping during VT

identified the earliest ventricular activation site at the

posteroapical LV septum, with an activation time of

−25.5 ± 3.1 ms, relative to the onset of the QRS complex

in all patients. The LDPs preceding PP were recorded

serially from the upper third to the middle of the LV septum

along the narrow longitudinal line in four patients in whom

ventricular mapping with the eight-pole catheter was per-

formed (Fig. 1). The LDP appeared earlier as the recording

site became closer to the base of the LV. At the middle or

lower third of the LV septum, the LDP appeared latest and

was fused with PP. We used the earliest LDP in measuring

the local conduction times. The LDP-PP, PP-VP and

VP-LDP intervals at the earliest LDP recording site were

68.5 ± 24.3 ms, 21.4 ± 7.2 ms and 256.3 ± 39.1 ms,

respectively, and the duration of the LDP was 21.5 ±

3.4 ms.

Effects of lidocaine and verapamil on local conduction
times and VT cycle length. In all patients but one, neither

lidocaine nor verapamil terminated VT. After lidocaine

(1 mg/kg per min), the VT cycle length significantly

increased from 355.3 ± 50.6 to 377.5 ± 45.3 ms (p < 0.01

vs. control). The LDP-PP increased from 77.7 ± 18.9 to


Abbreviations and Acronyms

ILVT = idiopathic left ventricular tachycardia
LDP = late diastolic potential
LV = left ventricular
PP = Purkinje potential
RV = right ventricular
RVA = right ventricular apex
RVOT = right ventricular outflow tract
st = stimulus
VP = ventricular potential
VT = ventricular tachycardia

pole electrode catheter with a 2.5-mm interelectrode inter-

(a = 4) was retrogradely inserted into the LV to perform

endocardial mapping during VT to identify the earliest

ventricular activation site and to record LDP by recording

electrograms from each electrode pair. All bipolar

electrograms were filtered between a bandpass of 50 and

and recorded simultaneously with three or six ECG

leads (I, II, III, aVF, V1 and V5) with the use of a polygraph

(Cardiolab system, Prucka Engineering, Houston, Texas).

Ventricular pacing was performed at a stimulus strength of

twice the diastolic threshold and with a pulse width of 2 ms,

using a programmable stimulator (SEC-3102, Nihon Ko-

den, Tokyo, Japan).

Entrainment from RVOT. Only the quadripolar catheter

was used to record LDP in the entrainment study, because

we could not stabilize the position of the eight-pole elec-

trode catheter in the LV, and thus we could not record

stable LDP during the entrainment study. We positioned

the tip of the quadripolar catheter at the earliest LDP

recording site and used this LDP in measuring local

conduction times during entrainment as well as during VT.

In all patients, entrainment of VT by pacing from the

RVOT at a rate 5 to 10 beats/min faster than the induced

VT rate was attempted while recording the LDP. When

VT was still present after termination of the pacing, rapid

pacing was again performed, with an increase in the pacing

rate by 5 to 10 beats/min. This procedure was repeated until

VT was interrupted or pacing reached the rate of 40 to 50

beats/min faster than the VT rate. In the last entrained beat,

the intervals from the stimulus artifact to the electrogram at

the RV apex (st-RVA) and from the stimulus artifact to the

LDP (st-LDP), as well as that from the LDP to PP

(LDP-PP), were measured at every pacing rate.

Effects of lidocaine and verapamil during entrainment.

During VT, lidocaine (1 mg/kg body weight over 1 min)

was intravenously administered in six of eight patients, and

the entrainment study was repeated. Approximately 15 min

after the lidocaine study, when the VT rate and local

conduction times returned to the control values, a small dose

of verapamil (0.5 mg) was intravenously administered to all

patients. When the VT rate was not decreased by about 20

beats/min, another dose of 0.5 mg (total dose 1.0 mg) was

administered. The entrainment study was repeated in seven

of eight patients. In the remaining one patient, verapamil

(1.0 mg) resulted in VT termination, and the entrainment

study was not performed. Throughout the study, we held

the catheter carefully to avoid applying pressure at the tip of

the catheter.

Before and after injection of each antiarrhythmic agent,

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using a dummy variable to encode the treatment condition

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(1 mg/kg per min), the VT cycle length significantly

increased from 355.3 ± 50.6 to 377.5 ± 45.3 ms (p < 0.01

vs. control). The LDP-PP increased from 77.7 ± 18.9 to
99.2 ± 17.0 ms (p < 0.05 vs. control), whereas PP-VP and VP-LDP remained unchanged. After verapamil (0.5 or 1.0 mg), the VT cycle length increased from 347.0 ± 52.4 to 394.6 ± 60.1 ms (p < 0.01 before verapamil), which was significantly greater than that after lidocaine (p < 0.05), and LDP-PP also increased from 76.3 ± 28.2 to 118.9 ± 34.1 ms (p < 0.01 before verapamil), which was significantly greater than that after lidocaine (p < 0.05), whereas PP-VP and VP-LDP remained unchanged. The LDP duration did not significantly change after lidocaine and verapamil. The increases in the VT cycle length after lidocaine and verapamil significantly correlated with those in LDP-PP (r = 0.98, p = 0.0006 for control study vs. post-lidocaine; r = 0.93, p = 0.0009 for pre-verapamil vs. post-verapamil) (Fig. 2). Neither of them was correlated with the change in PP-VP (r = 0.18, p = 0.74 for control vs. after lidocaine; r = 0.10, p = 0.81 for pre-verapamil vs. post-verapamil) or the change in VP-LDP (r = 0.17, p = 0.75 for control vs. after lidocaine; r = 0.53, p = 0.18 for pre-verapamil vs. post-verapamil).

In one patient, verapamil induced a beat-to-beat variation in both the VT cycle length and LDP-PP and terminated VT, with local conduction block between the LDP and PP recording sites (Fig. 3). Both PP-VP and VP-LDP were

Figure 1. Examples of late diastolic potentials (LDPs) (arrows) preceding Purkinje potential (PP) in four patients (cases 1, 4, 5 and 6), recorded serially from the middle to upper third of the left ventricular (LV) septum along the narrow longitudinal line during ventricular tachycardia (VT). Tracings are electrocardiographic leads I, II and V1, and intracardiac electrograms are recorded from the His bundle region (His), right ventricular apex (RVA), right ventricular outflow tract (RVOT) and eight-electrode catheter located in the LV septum (LV1 to LV8). All numbers are in ms. A = atrial potential; H = His bundle potential.

Figure 2. Correlations of the increases in VT cycle length (ΔCL) with those of the intervals from LDP to PP (ΔLDP-PP) after lidocaine (1 mg/kg) and verapamil (0.5 or 1.0 mg). There were significant correlations between the increases in VT cycle length and those in LDP-PP after lidocaine and verapamil (r = 0.98, p = 0.0006 for control study vs. post-lidocaine; r = 0.93, p = 0.0009 for pre-verapamil vs. post-verapamil). Abbreviations as in Figure 1.
almost constant after verapamil administration. The VT cycle length was significantly correlated with LDP-PP \( (r = 0.99, p = 0.0001) \), although not with PP-VP \( (r = 0.19, p = 0.65) \) or VP-LDP \( (r = 0.08, p = 0.85) \).

**Ventricular tachycardia entrainment and the effects of lidocaine and verapamil.** In all patients, entrainment phenomena, including constant fusion, except for the last entrained beat, and progressive fusion, were demonstrated by rapid pacing from the RVOT. A long conduction interval between the pacing site and the earliest ventricular activation site, indicating a slow conduction zone, was demonstrated during entrainment.

We also performed VT entrainment while recording the earliest LDP and examined the effects of lidocaine and verapamil. The LDP was captured orthodromically during entrainment, whereas the ventricular potentials at the LDP recording site and RVA were captured antidromically. The st-LDP and LDP-PP, which were measured in the last entrained beat, were 319.1 ± 34.8 ms and 81.9 ± 34.8 ms, respectively, at the pacing cycle length of 320.7 ± 49.6 ms. The st-RVA was 58.8 ± 14.1 ms. It is noted that st-LDP was much longer than LDP-PP, and the percentages of st-LDP and st-RVA to the interval from the stimulus artifact to PP, which was measured in the slowest pacing rate, were 80 ± 5% and 20 ± 5%, respectively (Table 1). When the pacing rate was increased, LDP-PP was prolonged, whereas st-LDP and st-RVA remained unchanged in all patients.

Figure 4 shows an example of the effects of lidocaine and verapamil on st-LDP, LDP-PP and st-RVA measured during entrainment. During the control study, st-LDP, LDP-PP and st-RVA were 370, 112 and 40 ms, respectively. After lidocaine administration, LDP was again captured orthodromically, and LDP-PP was prolonged to 168 ms, whereas st-LDP and st-RVA remained unchanged. After verapamil administration, LDP was captured orthodromically, and LDP-PP was further prolonged to 212 ms, whereas st-LDP and st-RVA remained unchanged. The effects of lidocaine \( (n = 6) \) and verapamil \( (n = 7) \) on local conduction times measured during entrainment are shown in Table 1. In all patients, LDP-PP measured during entrainment was prolonged after lidocaine and was further prolonged after verapamil, although the pacing rate used for entrainment was lower, especially after verapamil, as compared with that during the control study. The st-LDP and st-RVA remained unchanged. The relationship between the LDP-PP interval and pacing rate was compared between the conditions during the control study and those after verapamil administration, by using multiple linear regression. The regression equation was expressed as follows: when LDP-PP was named “Y” and the pacing rate “X,” \( Y = -255.56 + 44.25S_1 + 32.38S_2 + 129.74S_3 - 88.28S_4 - 43.53S_5 + 74.40S_6 - 95.92S_7 + 2.04X + 12.91D - 0.294X \times D \). In this equation, D is a dummy variable to encode before verapamil \( (D = 1) \) and after verapamil \( (D = 0) \)
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LDP = late diastolic potential; LDP-PP = interval from LDP to Purkinje potential (PP); RVA = right ventricular apex; st = pacing stimulus; st-LDP = interval from pacing stimulus to LDP; st-RVA = interval from pacing stimulus to electrogram at RVA.
S1 through S7 are subject dummy variables; the number 12.91 in the term 12.91D is an intercept shift caused by verapamil; and 0.294 in the term 0.294X represents a verapamil-induced change in the slope in which p = 0.0078. From these findings, the increase in LDP-PP in response to the increase in the pacing rate was augmented after verapamil administration.

**DISCUSSION**

In this study, LDP preceding PP was recorded serially from the upper third to the middle of the LV septum along the narrow longitudinal line during VT. The earliest LDP was recorded at the base of the LV septum, whereas the latest LDP recorded at the middle or lower third of the LV septum was fused with PP. We measured the local conduction times with the use of the earliest LDP and found that the interval from the LDP to PP increased during entrainment in response to an increase in the pacing rate, whereas the st-LDP interval was constant. Thus, it is suggested that the earliest LDP reflects the excitation at the entrance of a “specific” component of slow conduction, and the following serially recorded LDPs might represent the serial excitations in this component.

**Effects of lidocaine and verapamil on VT cycle length.** A small dose of verapamil and lidocaine selectively suppressed the

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**Figure 4.** Examples of entrainment by pacing from the RVOT at a rate of 145 beats/min while recording LDP during the control study (upper panel), after lidocaine administration (middle panel) and after verapamil administration (lower panel). Tracings are ECG leads I, II and V1, and intracardiac electrograms are recorded at the His bundle region (His), RVOT, RVA and LDP site (arrows). All numbers are in ms. The numbers in circles indicate conduction intervals from the LDP stimulus artifact (st) to the electrogram at the RVA and from LDP to PP. See text for discussion. Abbreviations as in Figure 1.
Conduction through the distal component, but neither of them affected the conduction in the proximal component, because LDP-PP was prolonged by the drugs, although PP-LDP was not. The increments in the VT cycle length after administering these drugs were correlated with those in LDP-PP. Furthermore, in one patient, verapamil induced a beat-to-beat variation of the VT cycle length and LDP-PP interval and terminated VT, with local conduction block within the distal component. We held the catheter carefully throughout the study to avoid applying pressure at the tip of catheter, because pressure could cause the same phenomenon (7). Thus, verapamil and lidocaine slowed the VT rate by selectively suppressing the conduction through the distal component.

**Ventricular tachycardia entrainment and the effects of lidocaine and verapamil.** To further elucidate this issue, we performed entrainment while recording LDP before and after lidocaine and verapamil administration. We found that verapamil selectively suppressed the conduction through the distal component, because LDP-PP, but not st-LDP, was prolonged after verapamil. The magnitude of the increase in LDP-PP with an increase in the pacing rate was augmented after verapamil. Thus, it is further confirmed that the target site of verapamil is confined to the distal component. This study also showed that lidocaine slightly but significantly suppressed the conduction through the distal component. The present dose of lidocaine is unlikely to affect conduction within the normal myocardium, unless the pacing rate is sufficiently high, but it might suppress conduction through the myocardial cells with partially depolarized membrane potential (13,14). These findings suggested that the main cellular mechanism of the conduction through the distal component is calcium channel-dependent and also involves depressed sodium channel-dependent tissue.

In contrast, the conduction through the proximal component was affected by neither lidocaine nor verapamil, suggesting that the cellular mechanism of the proximal component is sodium channel-dependent (normal). The conduction time through the proximal component was relatively long and occupied 80 ± 5% of the total conduction time from the stimulus artifact to PP during entrainment. Anatomically, it reflects conduction from the RVOT to the upper LV septum, and the distance was ~3 to 4 cm at most, if measured directly. In general, conduction velocity through tissue with normal sodium channel-dependent conduction is expected to be faster than that through tissue operated by the other cellular mechanism (13). Thus, the conduction velocity in this proximal component is too slow to be explained by the conduction through the normal ventricular tissue with normal sodium channel-dependent conduction. It was reported that the conduction velocity of a fiber is reduced as the diameter is decreased and the length is increased (15). Thus, we submit a hypothesis that the excitation in the proximal component is conducted along an anatomically isolated, long, thin pathway, such as the transverse LV false tendon. This structure, which extends from the posteroinferior LV to the LV septum, in many cases, was reported to be related to ILVT (16,17). Further studies are required to clarify this issue.

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