The role of β-blockade therapy for ventricular tachycardia induced with isoproterenol: A prospective analysis

Isoproterenol is sometimes required for ventricular tachycardia (VT) induction. However, the role of β-blockade for treatment of such VT has not been critically assessed. The use of β-blockade was evaluated prospectively in 14 consecutive patients who required isoproterenol 2.4 ± 1.3 (± S. D.) µg/min to induce sustained monomorphic VT (>30 seconds, or requiring termination due to hemodynamic collapse) after a negative baseline study. The VT mechanisms were enhanced automaticity (group A, six patients), triggered automaticity (group B, three patients), and reentry (group C, five patients). Groups A and B had serial intravenous electropharmacologic tests with propranolol alone (0.2 mg/kg), verapamil alone (0.15 mg/kg), and propranolol plus verapamil, and group C had serial tests with propranolol alone, procainamide or quinidine (class Ia drug) alone, and propranolol plus a class Ia drug until VT could no longer be induced. All six patients in group A responded to propranolol alone. In group B, one patient responded to verapamil alone, and two patients responded to propranolol plus verapamil. In group C, three patients responded to propranolol alone, one patient responded to a class Ia drug alone, and one patient responded to propranolol plus a class Ia drug. During a follow-up of 7 to 37 (17.9 ± 10.7) (± S. D.) months, VT has not recurred in any patient. Three patients treated initially with propranolol alone have required substitution of amiodarone due to refractory congestive heart failure. In patients requiring isoproterenol for VT induction, β-blockade alone appears to be effective in preventing reinduction of VT caused by enhanced automaticity. A heterogeneous response occurs when the VT mechanisms are triggered automaticity or reentry. (Am Heart J 1990;120:1347.)

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therapy for the induced VT has been based upon the VT mechanism.56 To date, a critical assessment of the role of β-blockade in the treatment of such dysrhythmias has not been undertaken. In this prospective study, the role of β-blockade therapy was evaluated in consecutive patients who required isoproterenol for initiation of VT after a negative baseline cardiac electrophysiology study.

METHODS

Patient population. Fourteen patients with recurrent, sustained monomorphic ventricular tachycardia were evaluated (Table I). There were five males and nine females, with an age range of 14 to 78 years. Three patients had coronary artery disease with a history of myocardial infarction, four patients had valvular heart disease, three patients had right ventricular dysplasia, one patient had hypertensive heart disease, and three patients had no clinical evidence of structural heart disease. Three patients had VT associated with physical exertion, and one patient had VT occur during extreme emotional distress.

Electrophysiology study protocol. Patients were studied in the postoperative, fasting state after discontinuation of antiarrhythmic therapy for at least 5 half-lives. Midazolam, 1 to 3 mg, was used intravenously for sedation. Three 6F quadripolar electrode catheters were inserted percutaneously into the right femoral vein and were positioned under fluoroscopic guidance against the high right atrium, the right ventricular apex, and across the tricuspid valve to re-
Fig. 1. Sustained ventricular tachycardia (VT) occurred spontaneously in this patient (No. 3) with enhanced automaticity during continuous intravenous isoproterenol administration. The coupling interval between the last sinus rhythm QRS and the first VT QRS varied from 340 to 420 msec (panels A, B, and C). After intravenous administration of propranolol, this VT did not recur spontaneously when isoproterenol was readministered nor could it be induced by programmed ventricular stimulation or ventricular overdrive pacing. Shown are a one-second (1 sec) time-line, surface electrocardiographic leads V1, I, and III, and intracardiac recordings of atrial (A), ventricular (V), and His bundle (H) activation from the proximal (p) and distal (d) high right atrium (HRA), His bundle electrogram (HBE), and atrial septum (SEP).

until refractoriness to $S_4$ occurred. $S_3S_4$ was then increased by 20 to 30 msec, and $S_2S_3$ was decreased in 10 msec intervals until refractoriness to $S_3$ occurred. After $S_2S_3$ was increased again by 30 msec, $S_1S_2$ was decreased in 10 msec intervals until refractoriness to $S_2$ occurred. After completion of programmed stimulation with $S_3S_4$ using two drive cycle lengths, ventricular burst pacing was performed using drive cycle lengths of 600 to 260 msec with drive trains of 15 cycles. The drive cycle length was decreased by 20 msec after each train was delivered. The inter-train interval was 3 seconds. Programmed stimulation at the right ventricular outflow tract was performed after completion of the protocol at the right ventricular apex.

**Infusion of isoproterenol.** After completion of programmed stimulation, isoproterenol was infused at rates of 0.5 to 4.0 $\mu$g/min (mean ± S. D. = 2.4 ± 1.3 $\mu$g/min). The spontaneous sinus cycle length decreased by 32 ± 13%. If VT did not occur spontaneously during isoproterenol administration, programmed stimulation was repeated at both right ventricular sites, as previously described.

**Definitions of mechanisms of induced ventricular tachycardia.** The following principles of clinical electrophysiology were utilized to classify the mechanisms of the induced VTs. Enhanced automaticity (group A). VT could not be induced by programmed stimulation but occurred spontaneously during isoproterenol infusion with varying coupling intervals between the last sinus rhythm QRS complex and the initial VT QRS complex. The initial VT QRS complex had the same morphology as the monomorphic VT. The VT could not be converted to sinus rhythm by overdrive pacing or programmed stimulation, and the VT morphology and cycle length did not change after overdrive pacing. Advancement of the first post-pacing VT QRS complex did not occur after overdrive pacing. The VT resolved only with discontinuation of isoproterenol.

Triggered automaticity (group B). VT could be initiated consistently over a specific range of cycle lengths during burst ventricular pacing without ventricular extrastimuli. The VT cycle length varied with the burst pacing cycle length. The first VT QRS complex occurred late in the cardiac cycle. This VT could be terminated by burst ventricular pacing.

Reentry (group C). VT was initiated with ventricular extrastimuli and could be terminated by overdrive pacing. Advancement of the first post-pacing VT QRS complex was sometimes observed when burst pacing or programmed extrastimuli failed to successfully terminate the induced VT.

**Electropharmacologic testing**

Groups A and B. During initial electropharmacologic testing, propranolol, 0.2 mg/kg, was administered intravenously and repeat testing was performed using the same dose of isoproterenol required to induce VT during the
Fig. 2. A through C. In this patient (No. 12) with triggered automaticity, sustained VT could be induced only by ventricular overdrive pacing during isoproterenol administration. VT was consistently induced by ventricular overdrive pacing at cycle lengths \( S_1S_1 \) of 340 and 360 msec (panels C and D), but not at cycle lengths greater than 380 msec (panels A and B) or less than 320 msec (panels E and F). This VT was not suppressed with intravenous propranolol alone or verapamil alone, but was suppressed with combined therapy with propranolol and verapamil. Ventricular electrograms from the right ventricular apex (RVA) are shown. Other abbreviations are the same as in Fig. 1.
minimum of 48 hours with intravenously administered procainamide or quinidine (10 mg/kg load and 0.06 to 0.075 mg/kg/min). If the class Ia drug did not suppress reinduction of VT, propranolol was readministered in a dose of 0.2 mg/kg and electropharmacologic testing was repeated.

All patients underwent final testing of orally administered drugs before hospital discharge to confirm that VT was not inducible using the previously described protocol before and during isoproterenol administration.

Follow-up. All patients were followed as outpatients with office visits every 2 to 3 months for the first 6 months, and with office visits or telephone contact every 3 months thereafter.

RESULTS

The results of electrophysiologic and electropharmacologic testing are summarized in Table I. All 14 patients required intravenous isoproterenol administration to induce sustained VT. Sustained mono-
Fig. 3. Initiation of sustained VT during isoproterenol administration in this patient (No. 10) with reentry consistently required three ventricular extrastimuli ($S_3S_3S_4$) during programmed ventricular stimulation (panel A), and was associated with a fall in blood pressure (BP). Ventricular overdrive pacing ($S_1S_1$) was uniformly successful in terminating this VT (panel B). Reinduction of this VT could not be suppressed by intravenous propranolol alone or quinidine alone. During testing of intravenous propranolol and quinidine in combination, only nonsustained VT with a maximum duration of seven cycles was induced by programmed ventricular stimulation (panel C). Abbreviations are the same as in Figs. 1 and 2.

Morphic VT (duration > 30 seconds, or requiring termination due to hemodynamic collapse) was induced a minimum of three times in each patient during isoproterenol administration. The spontaneous sinus cycle length during the baseline study was 840 ± 140 msec (mean ± S.D.). During continuous intravenous isoproterenol administration, the spontaneous sinus cycle length decreased to 570 ± 130 msec ($p < 0.05$, paired t test). During continued isoproterenol administration after intravenous administration of propranolol, the spontaneous sinus cycle length increased to 860 ± 100 msec ($p > 0.2$ versus...
the sinus cycle length during the baseline study) (paired t test).

Electrophysiologic testing. Six patients had enhanced automaticity (group A) (Fig. 1), three patients had triggered automaticity (group B) (Fig. 2), and five patients had reentry (group C) (Fig. 3).

Electropharmacologic testing. Overall, 9 of 14 patients (64%) had reinduction of VT suppressed by propranolol alone. Three of 14 (21%) patients required propranolol combined with other drug therapy to prevent VT reinduction.

Group A. All six patients with enhanced automaticity had reinduction of VT suppressed by propranolol alone.

Group B. None of the three patients with triggered automaticity had VT reinduction suppressed by propranolol alone. One patient had reinduction of VT suppressed by verapamil alone. Two patients had reinduction of VT suppressed by propranolol plus verapamil.

Group C. Three patients with reentry had reinduction of VT suppressed by propranolol alone. One patient had reinduction of VT suppressed by a class Ia drug alone, and one patient had reinduction of VT suppressed by propranolol plus a class Ia drug after failing to respond to a therapeutic serum concentration of the class Ia drug alone.

Follow-up. Follow-up has ranged from 5 to 37 (mean ± S.D. = 17.9 ± 10.7) months. VT has not recurred spontaneously in any patient. Three patients treated initially with propranolol alone developed refractory congestive heart failure despite preload and afterload therapy. Because of its indirect β-blocking effects and negligible negative inotropic effects when administered orally, amiodarone was substituted.6 None of these three patients had inducible VT after 10 days of oral loading (800 mg twice a day), and no patient has had a spontaneous recurrence of VT during long-term oral amiodarone administration (200 mg daily).

DISCUSSION

Isoproterenol is commonly used to facilitate the induction of clinically significant VT when it cannot be induced by standard ventricular programmed stimulation or burst ventricular pacing.1-6 As observed in this and earlier studies, many of these patients' VTs are not necessarily exercise-induced.5,6 The number of patients requiring isoproterenol to initiate VT make up a small proportion of the total number of patients whose VT is induced in the cardiac electrophysiology laboratory. Of the patients whose VT requires isoproterenol for initiation, a smaller proportion have coronary artery disease when compared with those patients who do not require isoproterenol for VT induction.6

The presence of both β1 and β2-adrenoreceptors in the human heart has been demonstrated by radioligand studies.9,10 Both receptor subtypes appear to be involved in increasing tissue levels of cyclic adenosine monophosphate.11,12 Isoproterenol is a nonselective agonist, whereas propranolol is a nonselective antagonist of both β1 and β2 receptors.13,14 The potential role that these receptors have in mediating activation of each VT mechanism is discussed separately.

Enhanced Automaticity. Spontaneous depolarizations occur most commonly in cells with slow-response action potentials.15,16 In isolated cardiac fiber models of spontaneous automaticity, the number of functionally slow channels appears to depend upon cyclic adenosine monophosphate (cAMP). During resting conditions, therefore, there may not be sufficient slow inward current to cause slow-response action potentials to occur.17 In this setting, it would be anticipated that β-receptor stimulation with isoproterenol might cause automatic VT to occur. Conversely, propranolol would be expected to be effective in suppressing such an automatic dysrhythmia. In the present study, all patients with VT due to enhanced automaticity had VT reinduction suppressed by β-blockade. Sung et al.18 have previously reported the failure of verapamil to suppress VT due to catecholamine-sensitive automaticity, and have postulated that this dysrhythmia may not be caused by a slow channel mechanism that is calcium-dependent in humans.

Triggered Automaticity. Triggered automaticity caused by delayed afterdepolarizations has been described previously in human tissues.19 In experimental models, intracellular calcium overload has been observed to occur during sympathetic stimulation. Subsequent oscillatory release of calcium by the sarcoplasmic reticulum activates a nonselective ion channel utilizing a transient sodium current and modulated by calcium.20-24 Of interest, one of the three patients in the present study had triggered automaticity activated by both ventricular extrastimuli and ventricular overdrive pacing. In vitro and in vivo studies have demonstrated a dependence upon a critical range of drive rates or coupling intervals for initiation, a cycle length that varies with the cycle length of the train of stimuli causing initiation, and termination by overdrive pacing, probably due to enhancement of sodium extrusion and membrane hyperpolarization.25

Both calcium channel antagonists and β-receptor blockers have been demonstrated to reduce calcium overload and block the calcium transient. These ac-
tions result in either reduction of both the action potential and the amplitude of delayed action potentials, or in prevention of delayed afterdepolarization altogether. In the present study, however, the administered intravenous doses of propranolol alone and verapamil alone were insufficient for uniformly suppressing triggered automaticity activated by isoproterenol. In two of the three patients with triggered automaticity, the synergistic effects of β-adrenoceptor blockade and calcium channel antagonism appeared to be necessary to suppress reinduction of VT.

Reentry. Reentry is a dynamic process that requires an area of unidirectional impulse block and recirculation of the impulse to its original point of block. When reentry cannot be initiated during resting conditions, the discrete responses of individual cardiac fibers to isoproterenol stimulation may create the milieu for reentry to occur. Under such conditions, differential shortening of the refractory period of individual fibers caused by isoproterenol provides a course for impulse propagation along fibers that have a shorter refractory period, and blocking in one direction in fibers having a longer refractory period.

In the presence of isoproterenol, β-blockers in concentrations causing β-blockade alone can reverse isoproterenol's accelerating effects on repolarization. The inability to reinduce reentrant VT after propranolol administration in three of the five patients in the present study may have been due to this phenomenon. In addition to competitive inhibition of catecholamine binding at β-receptor sites, β-blockers have been demonstrated to exhibit direct membrane-stabilizing action, i.e., "quinidine-like" blockade of the inward sodium current. However, this latter action has been observed only at concentrations that are up to 100 times greater than the clinical concentrations causing β-blockade.

Comparison with previous studies. Few studies have critically evaluated the role of β-blockade in suppressing VT that requires isoproterenol for its activation. Some studies have utilized intravenous doses of propranolol that may have been too small to effect adequate blockade or isoproterenol during electropharmacologic testing, or have not routinely tested propranolol in consecutive patients. One study has reported upon the long-term effectiveness of empirical oral β-blocker therapy for patients requiring isoproterenol for facilitation of VT induction during extrastimulus testing. However, only two of the nine patients in that study had sustained VT induced prior to antiarrhythmic therapy. To our knowledge, the present study is the first to prospectively evaluate the role of β-blockade in consecutive patients requiring isoproterenol for induction of sustained VT.

Conclusions. In patients requiring isoproterenol for ventricular induction, β-blockade alone appears to be effective in preventing reinduction of VT caused by enhanced automaticity. A heterogeneous response occurs when the VT mechanisms are triggered automatically or reentry. The similarity of the sinus cycle lengths measured after treatment with intravenous propranolol treatment during continuous isoproterenol administration, when compared with the sinus cycle lengths measured during the baseline study, suggests that adequate blockade of isoproterenol's β-agonistic effects should have been achieved with the dose of propranolol administered in this study. The failure of propranolol alone to uniformly suppress all VT activated during isoproterenol administration in this study could have several possible explanations. These include: (1) differences in the total number and the ratio of the subtypes of β-adrenoceptors that mediated activation of VT mechanisms in individual patients; (2) differences in the affinity of these receptors for propranolol and/or isoproterenol when compared with normal human cardiac β-receptors; and (3) differences in the intrinsic activity of individual patient's β-receptors in response to isoproterenol and/or propranolol. Patients who did not respond to intravenously administered propranolol were not retested during long-term oral propranolol administration. Therefore it is possible that the failure of immediate and complete β-blockade to suppress VT reinduction may not have predicted the results of long-term therapy. Further investigation will be necessary to substantiate the findings of the present study and to better define the role of β-adrenoceptor activation and blockade in human VT mechanisms.