Esmolol Tilt Testing With Esmolol Withdrawal for the Evaluation of Syncope in the Young

Marc Ovadia, MD, David Thoele, MD

Background
Head-upright tilt (HUT) testing is valuable in evaluating syncope. Isoproterenol is used to increase sensitivity. However, isoproterenol is contraindicated or dangerous in undiagnosed heart disease and produces false-positives. We introduced esmolol withdrawal during esmolol HUT, hypothesizing that (1) acute withdrawal of the ultrashort-acting β-blocker induces β-adrenergic effects by unmasking endogenous catecholamines and may provoke syncope with fewer risks, and (2) response to esmolol/esmolol withdrawal may predict effective therapy.

Methods and Results
Thirty-six patients with unexplained recurrent syncope/presyncope (7 to 35 years old, known heart disease or arrhythmia in 14) underwent 2 to 4 HUT tests (60', 49 minutes): (1) baseline, (2) esmolol (500 µg/kg plus 50 µg·kg⁻¹·min⁻¹), (3) esmolol withdrawal (HUT continued after esmolol stopped), and (4) isoproterenol if tests 1 through 3 were negative and isoproterenol was not contraindicated. A positive test reproduced symptoms with hypotension or bradycardia, requiring recumbency for recovery. Twenty-five had positive tests, and 11 had negative tests. In 5, only the baseline test was positive; in 15, esmolol/esmolol withdrawal tests were also positive, with 3 in whom esmolol withdrawal was positive although negative at baseline. Two isoproterenol tilts were positive. Esmolol withdrawal and isoproterenol tilts had the highest initial heart rate and similar maximal heart rate increment. Only isoproterenol caused hypertension. One isoproterenol test was false-positive, with hypertension-induced arterial baroreflex. Treatment was β-blockers (8), Na/fludrocortisone (9), both (6), and DDD pacemakers (2). Esmolol/esmolol withdrawal accurately predicted therapeutic response in 15; isoproterenol predicted therapeutic response in none.

Conclusions
Esmolol withdrawal tilt testing is preferable to isoproterenol for provocative testing of syncope in the young, and it appears to be safer. Esmolol withdrawal testing has clinical utility before invasive testing as a first-line investigation for syncope in patients with or without heart disease.

Key Words
- hypotension
- syncope
- nervous system
- receptors, adrenergic, beta

Although isoproterenol may be effective in provoking syncope in HUT protocols, addition of isoproterenol is not without disadvantages. Isoproterenol is contraindicated or hazardous in many patients with heart disease because of its arrhythmogenic and β-adrenergic properties, which may cause hemodynamic decompensation in patients with tachycardias, severe hemodynamic lesions (eg, obstruction), or ischemic heart disease. Because isoproterenol is a vasodilator and a positive chronotopic agent, bradycardia may be masked and hypotension accentuated. Last, isoproterenol causes syncope in up to 45% to 65% of volunteers with no history of syncope; thus, specificity may be unacceptably low. These disadvantages and risks of isoproterenol have caused a reevaluation of its use in tilt testing, and many laboratories restrict isoproterenol for patients with structurally normal hearts who have already undergone both invasive electrophysiologic testing and hemodynamic catheterization with negative results.

In this investigation, an alternative approach to isoproterenol is presented for provocative catecholamine testing of syncope. This approach uses withdrawal of an ultrashort-acting β-blocker, esmolol, during tilt testing as a form of β-adrenergic stress. Endogenous catecholamines at physiological levels rather than exogenous catecholamines at pharmacologic doses amplify the adrenergic stress of HUT. Esmolol withdrawal during tilt provokes syncope by unmasking endogenous epinephrine and norepinephrine elicited by HUT, possibly with fewer deleterious side effects than for isoproterenol. The hypothesis of this investigation is twofold: (1)
that as a form of β-adrenergic stimulation, acute withdrawal of esmolol during HUT has fewer side effects and disadvantages (including false-positives) than isoproterenol, and (2) that the response to acute testing with a β-blocker and during β-blocker withdrawal will facilitate clinical management.

Methods

Patient Selection and Evaluation

The patient population consisted of consecutive individuals with unexplained recurrent syncope or presyncope who underwent HUT. All were evaluated by history and physical examination. Individuals with isolated upright syncope triggered by surprise or fright, resolving promptly on recumbency, were excluded. (Vasovagal syncope was diagnosed presumptively in such patients on clinical grounds if there was no evidence of structural heart disease or arrhythmia by clinical evaluation, two-dimensional echocardiography, and Holter monitoring.)

Evaluation included physical examination with blood pressure measurement with the patient supine, sitting, and standing; 12-lead ECG; two-dimensional echocardiography, and 24- to 48-hour Holter monitoring as indicated. An exercise test using the Bruce protocol was completed by those who had symptoms with exercise.

HUT was recommended as a diagnostic test before consideration of catheterization, electrophysiological testing, or treatment in patients in whom historic features were atypical or idiosyncratic for simple fainting and clinical evaluation was not diagnostic.

Tilt Testing

Patients underwent two to four head-upright (60°) tilt tests lasting up to 49 minutes each, including (1) baseline tilt, (2) esmolol tilt (after esmolol 500 μg/kg intravenously over 2 to 5 minutes, followed by 50 μg·kg⁻¹·min⁻¹ intravenous infusion), (3) esmolol withdrawal tilt (tilt continued after esmolol stopped), and (4) isoproterenol tilt if tests 1 through 3 were negative and there were no contraindications to isoproterenol (eg, possible significant hemodynamic lesion, supraventricular or ventricular tachycardia, ischemia, or severe hypertension). Between tests, the patients rested supine for 20 to 60 minutes. See Table 1.

Testing was started at midday 30 to 60 minutes after placement of an intravenous cannula. Noninvasive continuous ECG and blood pressure monitoring were used (Quinton Q-5000, Colin Pulsenate BX-5). Studies were performed in a darkened room with no threatening equipment visible to the patient after 20 to 60 minutes of rest in the supine position. A motorized tilt table with foot-plate support was used. Transit time from 0° to 60° was 23 seconds.

Baseline tilt was maintained for 49 minutes or until syncpe or intolerable symptoms developed, at which time the patient was returned to the supine position, and noxious stimulation was initiated to determine the moment of recovery of consciousness. After this 49-minute baseline tilt test, the esmolol protocol was initiated.

The esmolol tilt test was performed after supine rest for 20 to 30 minutes. Esmolol (Brevibloc) was administered intravenously with a 500-μg/kg loading dose over 2 to 5 minutes followed by continuous infusion at a rate of 50 μg·kg⁻¹·min⁻¹. The infusion rate was increased by up to 20% every 3 to 5 minutes. The 60° head-upright tilt was initiated after 3 to 10 minutes, when heart rate was stable. Esmolol HUT was maintained either for 15 minutes (if baseline HUT was negative) or for the full time of baseline tilt plus 5 to 10 minutes (if baseline tilt test was positive) or until syncpe. If tilt was stopped for symptoms during esmolol infusion, the patient was returned to the supine position, and esmolol was tapered gradually to avoid esmolol withdrawal effects.

Table 1. Protocol of Tilt Testing

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<tr>
<td>1</td>
<td>Rest</td>
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<td>2</td>
<td>Baseline tilt</td>
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<tr>
<td>3</td>
<td>Rest</td>
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<td>4</td>
<td>Esmolol tilt</td>
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<td>5</td>
<td>Esmolol withdrawal tilt</td>
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<td>6</td>
<td>Rest</td>
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<tr>
<td>7</td>
<td>Isoproterenol tilt</td>
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</table>

Esmolol withdrawal HUT was then performed. At the end of the esmolol tilt, esmolol infusion was discontinued acutely while maintaining the tilt. The esmolol withdrawal tilt was continued for an additional 29 minutes or until syncpe or intolerable symptoms occurred.

The isoproterenol tilt test was performed if the three previous tests were negative and there were no contraindications to isoproterenol. At the point of at least 5 half-lives free of esmolol (esmolol mean half-life, >4 to 9 minutes in different age groups), isoproterenol was given at 0.01 μg·kg⁻¹·min⁻¹, titrated upward every 1 to 2 minutes to target heart rate ≥120% of baseline. The 60° head-upright tilt was initiated. Infusion was reduced for heart rate >150 beats per minute. Tilt was continued 15 minutes or until syncpe or intolerable symptoms occurred.

Responses to HUT

A positive test reproduced symptoms in association with hypotension or bradycardia and required recumbency for recovery. If the patient had transient symptoms that did not require recumbency for recovery, HUT was continued, and this was considered a transient positive response. Syncpe was considered to be false-positive if severe hypertension preceded and provoked the vagal reaction, indicating that this represented a normal arterial baroreceptor reflex. If a patient required cardiopulmonary resuscitation or transectaneous pacing for resolution of symptoms, the patient was considered positive for that HUT, but the protocol was aborted.

There are seven possible patterns of test results: (1) all negative tests, (2) positive baseline but all negative provocative tests, (3) negative or (4) positive baseline and positive esmolol tilt, (5) negative or (6) positive baseline tilt and negative esmolol but positive esmolol withdrawal tilt, and (7) first three tilt tests were negative but with a positive isoproterenol tilt. These responses to provocations predict β-blocker-responsive syncope in groups 5, 6, and 7 and β-blocker-nonresponsive syncope in groups 3 and 4.

Medications were or were not given after discussion with the patient and the patient’s parents and at the discretion of the
study physicians. Follow-up every 3 to 6 months was scheduled.

**Data Analysis**

For each of the four different tilt groups, systolic and diastolic blood pressures, heart rate, respiratory rate, and heart rate were recorded for the immediate pretilt, immediate posttilt, immediate presymptomatic period, and symptomatic period when the test was terminated, as well as for every 30 to 60 seconds during the tilt before symptoms and termination. Fisher one-factor ANOVA was used to compare the following variables among the several groups: initial heart rate and systolic blood pressure; initial change (increment or decrement) in heart rate; systolic and diastolic blood pressures upon tilt; maximal heart rate during tilt; maximal increment of heart rate during tilt; and maximal systolic blood pressure during tilt. Student-Newman-Keuls q test (SNK) was used for comparisons between groups. The Fisher exact test was used for analysis of 2×2 contingency tables.

**Results**

**Patient Population**

The study population included 36 patients with unexplained recurrent syncope or presyncope despite standard workup. The patients ranged in age from 7 to 35 years, with a median age of 14 years. All except 2 were 10 to 19 years of age. Twenty-seven patients had syncope, and 9 had presyncope. Eight of the patients with syncope also had seizures associated with the syncope. No patient had isolated loss of consciousness triggered by fright or surprise (simple fainting). Two-dimensional echocardiography was performed in 32, and 24- to 48-hour Holter monitoring was performed in 28. Those with symptoms during exercise underwent treadmill testing; treadmill results were nondiagnostic in all. Seven had heart disease believed not to be hemodynamically significant. Six of the children with heart disease and an additional 7 without structural heart disease had arrhythmias or conduction system disturbances believed not to be causing syncope (2 had pacemakers). A total of 111 HUT tests were performed in the 36 patients. See Table 2.

**Heart Rate and Blood Pressure Responses to Tilt**

All 36 patients underwent baseline tilt, 35 underwent esmolol tilt, 28 underwent esmolol withdrawal tilt testing, and 12 had isoproterenol tilt (Table 1). One patient required cardiopulmonary resuscitation after the baseline tilt as a result of protracted asystole not responding promptly to recumbency (33 seconds); she did not undergo further study. See Table 3.

Initial heart rate was significantly higher (P<.0005, ANOVA) after esmolol withdrawal (84±11/min, mean±SD) and isoproterenol (108.8±23.3/min) than for baseline (71±13/min) and esmolol (70±14/min, P<.001). Initial systolic blood pressures were significantly different for the various groups (P<.01, ANOVA). Isoproterenol was associated with significantly elevated initial systolic blood pressure (118±26 mm Hg) relative to esmolol withdrawal (103±13 mm Hg, P<.05).

Upon HUT initial heart rate change, systolic and diastolic blood pressure changes were not significant in any of the four types of HUT procedure.

Maximal change in heart rate (always an increase) with HUT is a measure of the degree of induced

<table>
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<tr>
<th>Table 2. Patient Characteristics</th>
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<tr>
<td><strong>Number of patients</strong></td>
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<td><strong>Age, y</strong></td>
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<td>Median</td>
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<td>Range</td>
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<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
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<tr>
<td><strong>Symptom</strong></td>
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<tr>
<td>Syncope</td>
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<td>Syncope with convulsions</td>
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<td>Presyncope</td>
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<td><strong>Duration of symptoms, mo</strong></td>
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<td>Median</td>
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<td><strong>Number of syncopal episodes, mean</strong></td>
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<tr>
<td>Range</td>
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<tr>
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<td>Orthostatic hypotension</td>
</tr>
<tr>
<td><strong>Heart disease</strong></td>
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<td>Repaired tetralogy of Fallot (conduit)</td>
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<tr>
<td>Possible hypertrophy</td>
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<td>Mitral prolapse</td>
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<tr>
<td>Congenital complete heart block</td>
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<td>No heart disease</td>
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</table>

*These patients were evaluated for upright presyncope, not for other episodes of syncpe.
physiological stress. Fig I depicts the maximal heart rate change for the various protocols. Maximal heart rate change (supine to tilt) was 39.6±18 beats per minute in the baseline tilt, 27.7±15 beats per minute in the esmolol HUT, 38.5±17 beats per minute in the esmolol withdrawal HUT, and 26.1±17 beats per minute in the isoproterenol HUT.

Maximal heart rate achieved differed among the various HUT groups (P<.0005, ANOVA). Significant differences (P<.005) were noted between isoproterenol HUT (135±23/min) and each of the other HUT values. Maximal heart rate achieved equals the sum of initial heart rate and maximal heart rate change, which are analyzed separately above.

A significant difference in maximal systolic blood pressure was found among the HUT procedures (baseline, 124.9±17 mm Hg; esmolol, 117.9±18 mm Hg; esmolol withdrawal, 115.6±8 mm Hg; and isoproterenol, 138.3±22 mm Hg; P<.0005, ANOVA), with significant differences between isoproterenol and both esmolol withdrawal and esmolol (P<.001). In the first 24 patients, there were two instances of systolic hypertension with isoproterenol (180 and 170 mm Hg) but not with esmolol withdrawal (P<.05, Fisher exact).

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**Fig 1.** Bar graph: Maximum heart rate (HR) increment with tilt is used as a measure of induced physiological stress, including postural stress and β-adrenergic stimulation. This table compares maximum heart rate increment among the various tilt protocols in all patients who underwent each protocol. Each bar depicts the maximum heart rate increment (supine to tilt) of one of the tilt protocols. Isoproterenol is the standard β-adrenergic agent used to augment physiological stress induced by tilt. The efficacy of esmolol withdrawal (acute withdrawal of the ultrashort-acting β-blocker esmolol) as a provocative intervention during tilt as an alternative to isoproterenol is gauged by comparison of esmolol withdrawal to isoproterenol. Comparison demonstrates that the maximum heart rate increase with esmolol withdrawal tilt is as great or greater than that with isoproterenol tilt. This implies that esmolol withdrawal is as potent a stimulus as isoproterenol in augmenting the physiological stress induced by tilt or that esmolol withdrawal may be more potent.
Table 4. Results of Testing

<table>
<thead>
<tr>
<th>Group</th>
<th>Patterns of Test Results</th>
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<tbody>
<tr>
<td>1</td>
<td>All negative tests</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Positive baseline but all negative provocative tests</td>
<td>5</td>
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<tr>
<td>3</td>
<td>Negative baseline, positive esmolol tilt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Positive baseline, positive esmolol tilt</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Negative baseline, negative esmolol, positive esmolol withdrawal tilt</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Positive baseline, negative esmolol, positive esmolol withdrawal tilt</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Baseline, esmolol, esmolol withdrawal negative; positive isoproterenol test</td>
<td>2</td>
</tr>
</tbody>
</table>

Responses to provocation that predict β-blocker–responsive syncope include groups 5, 6, 7, and possibly 2. Responses that predict β-blocker–nonresponsive syncope include groups 3 and 4. The group 7 response may not be as useful a predictor of β-blocker–responsive syncope as other response patterns listed. See “Results” and “Discussion.”

Results of HUT Testing

Syncope or intolerable vagal symptoms were provoked in 25 of the 36 patients (positive test). Eleven patients had all negative tests. See Table 4.

In 23 patients the baseline, esmolol, or esmolol withdrawal tests were positive. In 2 patients, the isoproterenol test was positive but all the other tilt tests were negative.

Of the patients with at least one positive test, 5 had positive baseline tilt, 15 had positive baseline and positive esmolol or esmolol withdrawal tilt, 3 had negative baseline but positive esmolol or esmolol withdrawal tilt, and 2 had positive isoproterenol but negative baseline, esmolol, and esmolol withdrawal tilts.

The positive baseline tests became positive at less than 10 minutes in 5 of 20 patients only. In the specific group of 7 patients positive both at baseline and on esmolol withdrawal, 6 became positive during the baseline tilt only after 10 minutes.

In patients with any positive test, the precipitating cause of syncope was a depression of blood pressure with preserved (or elevated) heart rate in 19 and depression of heart rate or asystole in 6.

No patient had a positive test only during esmolol HUT (ie, negative baseline but positive esmolol). Such a pattern would be expected in false-positives as a result of a β-blocker.

A typical vagal response to esmolol withdrawal is shown in Fig 2. Tilt occurred at time t=0 and esmolol withdrawal shortly after t=30 minutes. After esmolol withdrawal, the heart rate increased. At 45 minutes, hypotension (71 mm Hg) was observed with symptoms of lightheadedness. The child required recumbency for recovery (48 to 49 minutes).

One isoproterenol positive was one of two tests that were falsely positive for vasovagal syncope because of transient hypertension (blood pressure, 180/120) precipitating a normal arterial baroreceptor reflex with hypotension.

Results suggested that 17 patients had syncope responsive to β-blocker, and 8 patients were unresponsive.

The 11 patients with all negative tests underwent further workup. In 2, severe hemodynamic lesions were found by catheterization (obstruction of a conduit in 1, dynamic left ventricular outflow obstruction caused by hypertrophic cardiomyopathy in 1). One of the 11 was transiently positive on baseline and negative on all subsequent tests: a false-positive baseline test because of hypertension and arterial baroreceptor reflex. In 2 patients who refused invasive workup, supraventricular tachycardia was observed and/or strongly suspected to be the cause of symptoms. Two patients had a psychiatric evaluation that suggested psychogenic symptoms (hysterical or Münchausen). The 4 remaining patients remain without diagnosis (1 despite catheterization and electrophysiological testing). None of these 11 had recurrent syncope in follow-up.

Treatment and Follow-up

The 25 patients with positive tests were placed on therapy according to the results of tilt testing: 9 on NaCl with or without fludrocortisone, 6 on β-blocker plus fludrocortisone, 8 on β-blocker, and 2 with DDD (AV universal) pacemakers.

Fifteen patients were subjectively improved with 9-month median follow-up (range, 4 to 21 months), 4 were worse, and 6 are lost to follow-up. There was no preponderance of any particular test result type in patients whose symptoms were worse. Except for positive isoproterenol tilt test responses, there was no particular hemodynamic response to tilt that failed to predict response to treatment.

Of 2 patients positive on isoproterenol and negative on all other tests, one was a false-positive previously mentioned; the other became worse (with increased presyncope) when given a β-blocker. Thus, both positive isoproterenol tilt tests appear to represent false-positives. Of course, these isoproterenol tilt tests were performed after baseline, esmolol, and esmolol withdrawal tilt tests were all negative, in accordance with protocol. In this context, isoproterenol tilt test positive response does not appear predictive of β-blocker–responsive syncope.

Esmolol and esmolol withdrawal accurately predicted therapeutic response in 15 patients, and isoproterenol predicted therapeutic response in none. For the 11
patients with all negative tests, no further recurrences of syncope occurred.

Complications

One patient had severe presyncope in the first half hour after completion of the test; the symptoms resolved promptly with recumbency. The only noteworthy complications of the study were episodes of hypertension in 4 patients (caused by isoproterenol in 2). The 2 patients falsely positive for syncope (provoked in both by isoproterenol) recovered without complications.

Discussion

The most important finding of this study is that esmolol withdrawal appears to be an effective or superior alternative to isoproterenol in head-upright tilt testing.

Esmolol Withdrawal

Esmolol withdrawal (acute withdrawal of esmolol during HUT) is a form of β-adrenergic stress involving endogenous catecholamines at physiological levels rather than exogenous catecholamines at pharmacological doses. Esmolol withdrawal during tilt provokes syncope by unmasking the endogenous epinephrine and norepinephrine elicited by HUT. These catecholamines then provoke syncope presumably by increasing cardiac contractility and thereby stimulating mechanosensitive vagal afferents, which reflexly lead to hypotension and bradycardia in a manner similar to that postulated for isoproterenol (and some spontaneous syncope).

Although previous authors have reported safe use of esmolol in children, its use in pediatric HUT has not been reported. Esmolol withdrawal during HUT as a form of β-adrenergic stress has not been reported for pediatric or adult patients. Esmolol use in adult HUT has been restricted to testing β-blocker effect during repeat tests in patients with a positive prior test in a manner similar to the use of intravenous propranolol or intravenous metoprolol.

Esmolol Withdrawal Versus Isoproterenol

The physiological effects of esmolol withdrawal are similar to isoproterenol, with important exceptions. Although the maximal heart rate is elevated with both isoproterenol and esmolol withdrawal, this increase is due to an increased supine heart rate in isoproterenol testing (caused by the β-adrenergic effects of isoproterenol while the patient is supine), but in esmolol withdrawal testing, the maximal heart rate change (supine to tilt) is increased. This suggests that esmolol withdrawal specifically augments the stress associated with HUT by unmasking the endogenous catecholamines epinephrine and norepinephrine released in response to tilt. Isoproterenol does not augment the stress of tilt, rather it adds a β-adrenergic stress independent of HUT. This effect is reflected in increased heart rate and systolic blood pressure in the supine position observed with isoproterenol, making isoproterenol tilt a poor model for spontaneous syncope and near syncope (which do not occur in the supine position). These findings further reflect the excessive (non-physiological) β-adrenergic stress associated with use of the exogenous β-adrenergic agent isoproterenol at pharmacological doses rather than the endogenous catecholamines at physiological levels with esmolol withdrawal. Indeed, with isoproterenol, systolic hypertension was documented in two instances, with a false-positive syncope caused by a normal arterial baroreceptor reflex in one of these patients. Neither of these effects were observed with esmolol withdrawal. (It may not be surprising that the arterial baroreceptor reflex is a source of false-positive syncope in HUT: Experimental feline work of Öberg and Thorén has previously shown that excitation of the arterial baroreceptor causes relatively greater depressor effect than stimulation of afferent cardiac vagal fibers.)

Esmolol testing with esmolol withdrawal during tilt may provide useful information on β-blocker responsiveness. Furthermore, no false-positive attributable to esmolol was found (ie, an instance where esmolol tilt was the only positive tilt), and no false-positives were attributed to esmolol withdrawal. However, one or both of the two isoproterenol positives were false-positives. This result supports the possibility that esmolol withdrawal may be more specific than isoproterenol in detecting mechanisms of spontaneous outpatient syncope. Isoproterenol appears to add negligible sensitivity to esmolol withdrawal testing, although it adds risks and disadvantages.

Safety of Esmolol and Esmolol Withdrawal

The esmolol and esmolol withdrawal protocols appear to be safe for evaluation of unexplained syncope, even in a group of patients with no exclusion criteria based on heart disease, arrhythmia, or conduction system disease. The safety of esmolol and esmolol withdrawal protocols is emphasized by the fact that these were used safely even in two children in whom later catheterization uncovered severe conduit obstruction with systemic right ventricular pressure in one and severe obstruction with provocation in a case of hypertrrophic cardiomyopathy in the other. Both children had appeared on repeated pretilt echocardiograms not to have significant hemodynamic derangements, the first because of a significant underestimate of conduit gradient that was due either to suboptimal acoustic window or to long segment stenosis, the latter because of minimal resting gradient. The fact that this protocol was safely used in these and other patients with history of significant heart disease supports further investigation of esmolol with esmolol withdrawal testing during HUT as a first-line diagnostic investigation before invasive testing for patients with or without heart disease. The esmolol and esmolol withdrawal protocols thus may have broader applicability than isoproterenol HUT.

Sensitivity and Specificity of the Protocols

It is a limitation of this study that sensitivity and specificity cannot be directly compared either between different protocols (eg, the esmolol/esmolol withdrawal protocol versus standard isoproterenol protocols) or in different populations (eg, patients versus normal subjects). However, certain observations may be made.

First, although this study is not a direct comparison of isoproterenol with esmolol/esmolol withdrawal, the study can address the question of whether isoproterenol tilt testing adds either sensitivity or specificity to the esmolol/esmolol withdrawal protocol. Isoproterenol tilt testing in patients with negative responses to baseline,
esmolol, and esmolol withdrawal tilt testing was either negative (n=10, in which case there was no diagnostic benefit from isoproterenol) or when positive, appeared to be characterized by false positivity in 2 such patients. Thus, no true positives were identified by isoproterenol testing. This suggests that in a group of patients such as this, isoproterenol adds no sensitivity and may reduce specificity. This supports and amplifies a similar conclusion of Kapoor and Brant.25 On the basis of these data, it appears that, without detriment to diagnostic accuracy, isoproterenol can be dispensable.

Second, the design of this protocol incorporates replication of positive test results, whereas standard isoproterenol tilt protocols (10-minute baseline tilt followed by isoproterenol if baseline is negative) may involve repeat testing only in the case of an initial negative test. This aspect of the protocol may impart significant benefit to diagnostic accuracy and statistical precision. The arduous character of the stimulation protocol (baseline, esmolol, and esmolol withdrawal), with replications, may be one reason for the low (or zero) rate of isoproterenol true positivity after this protocol is negative.

Finally, in the group of patients with positive baseline and esmolol withdrawal tilts, 6 of 7 became positive during the baseline tilt only after 10 minutes. Thus, there exists a group of patients negative on initial 10-minute baseline tilt who might be identified by esmolol withdrawal without recourse to isoproterenol. This is particularly relevant because esmolol withdrawal is applicable to patients with heart disease or arrhythmia, although isoproterenol is more limited in application.

Pediatric Versus Adult Protocols

The use of protocols similar to those of Almquist et al2 and Waxman et al19 (a 10-minute tilt followed by isoproterenol) requires catheterization of children including electrophysiological catheterization before tilt. Given the rarity of significant unanticipated positive findings on catheterization in children—particularly those with structurally normal hearts—compared with adults, who may have occult coronary disease, the use of an approach so similar to those validated in adults may imply exposure of children to unnecessary risks. Furthermore, there is the possibility of artifactualy positive findings, particularly in children with known incidental heart disease. The esmolol and esmolol withdrawal protocols reduce these risks and permit testing of syncope before recourse to invasive diagnostic tests. It must be noted, however, that our protocol involves a 49-minute baseline tilt, similar to the practice of Suttontal (from References 4, 5, and 8). Since only 5 of our 20 patients who were positive on baseline tilt became positive in the first 10 minutes, duration of baseline tilt in our protocol is also an important factor in the utility of the protocol. This prolonged baseline tilt, followed by esmolol withdrawal during esmolol tilt testing, may obviate the need for pretilt invasive diagnostic catheterization and intratilt isoproterenol.

Conclusions

In contrast to isoproterenol testing, esmolol withdrawal appears suitable as a first-line diagnostic investigation and screening modality before invasive testing even in patients with diagnosed (or undiagnosed) heart disease or rhythm disturbances. Finally, such a protocol could predict β-blocker responsiveness and assist in choice of medication in certain patients.

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