Rapid Publication

Cardiac Arrhythmias During Epinephrine-Propranolol Infusions for Measurement of In Vivo Insulin Resistance

RICHARD M. LAMPMAN, JOHN T. SANTINGA, DAVID R. BASSETT, AND PETER J. SAVAGE

SUMMARY

Sixty-eight determinations of in vivo insulin resistance were conducted in 35 males (aged 29–63 yr) by measurement of steady-state plasma glucose levels during a combined intravenous infusion of propranolol, epinephrine, glucose, and insulin. Subjects were mildly diabetic and/or hyperlipidemic. All were asymptomatic, denied taking medication, and had no history of cardiac disease. All had normal resting electrocardiograms. During the infusion, mean increases in systolic and diastolic blood pressure were 27 ± 12.2 ($\bar{x}$ ± SD) and 14 ± 5.7 mm Hg, respectively; mean reduction in heart rate was 19 ± 6.1 beats/min. Six out of the 35 subjects developed cardiac arrhythmias during the infusion test. Maximal exercise treadmill tests failed to predict all subjects who subsequently developed arrhythmias during the infusion test. These results suggest that this infusion test should be performed under continuous cardiac monitoring and promptly terminated if major arrhythmias develop.

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Evidence is increasing that resistance to insulin-mediated glucose disposal is a significant factor in the carbohydrate intolerance of many patients with type II, non-insulin-dependent diabetes mellitus.[1] It thus is becoming increasingly important for researchers to measure in vivo insulin resistance and to assess its relationship with glucose intolerance. Two major approaches to assess total body insulin resistance have been described[2–4] and several modifications have been reported recently.[5–7] This report describes potentially significant cardiac arrhythmias found during the infusion of propranolol and epinephrine, and calls attention to the need for caution when this technique is employed, especially in subjects with an increased risk of latent heart disease.

From the Department of Internal Medicine, Divisions of Cardiology, Hypertension, and Endocrinology and Metabolism, The University of Michigan, Ann Arbor, Michigan.

Address reprint requests to Richard M. Lampman, Ph.D., Department of Internal Medicine, Division of Cardiology, University of Michigan Medical Center, 1405 East Ann Street, Ann Arbor, Michigan 48109.

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MATERIALS AND METHODS

Thirty-five males aged 47.6 ± 8.6 yr (mean ± SD, range 29–63 yr) with percent ideal body weight (based on Metropolitan Life Insurance Tables, 1959) of 112 ± 14.7%, all asymptomatic and without a history of angina or previous myocardial infarction, were selected for this study on the basis of having abnormalities in either carbohydrate tolerance and/or lipid concentrations. All subjects had normal resting electrocardiograms (ECG) and denied recent medication ingestion before entry in the study. All tests were performed in the Clinical Research Center of the University of Michigan Hospital after an overnight fast. All but two of the subjects underwent tests of in vivo insulin resistance according to the method of Shen et al.[3] both before and after an intervention of exercise and/or diet. This report describes an unanticipated side effect of the test. To assess insulin resistance, 5 mg of propranolol was initially injected intravenously over a 1-min period, then followed by a continuous infusion of epinephrine (6 μg/min), propranolol (0.08 mg/min), glucose (6 mg/kg/min), and insulin (80 mU/min) for 150 min, using a constant infusion pump (Model #975, Harvard Apparatus Co., Inc., Millis, Massachusetts), into a forearm vein. Steady-state plasma concentrations of insulin and glucose were achieved by 90 min. The plasma concentrations of insulin and glucose then were measured every 10 min for 60 min on samples obtained from an indwelling needle placed in the opposite forearm. Before, during, and for 15 min after this test, blood pressure and heart rate responses of the patients were constantly monitored. Blood pressures were measured using manual auscultation. Heart rates and ECG patterns were monitored via a bipolar CM_5 (V_5 and manubrium) lead. These same cardiovascular measures were recorded for each patient during a prior maximal treadmill exercise test performed as previously described.[8] The exercise test was considered abnormal if there was ≥ 1-mm S-T segment depression with a horizontal or downsloped S-T segment or a 2-mm S-T segment depression 80 ms be-

yond the J point. Arrhythmias were recorded as present if there was at least one abnormal beat during the baseline or testing period. For this report, initial and final tests were combined for analysis.

RESULTS

Overall, 68 propranolol, epinephrine, glucose, and insulin infusion tests were performed. One of these tests was terminated prematurely. All patients displayed an elevation of blood pressure and reduction of heart rate during this procedure. Shown in Table 1 are the mean heart rate and blood pressure measurements for the 35 subjects taken at rest, at 10-min intervals between 90 and 150 min of these steady-state plasma glucose tolerance tests, and during prior treadmill exercise tolerance tests at the subjects' maximum level.

During the propranolol, epinephrine, glucose, and insulin infusion, significant lowering of heart rate ($P < 0.01$) and elevation of blood pressure ($P < 0.01$) were observed. While mean systolic blood pressure increased by 27.2 mm Hg during these tests, it never reached the peak mean value of 195 mm Hg found during maximum exercise testing. Mean diastolic pressure of 92.1 mm Hg during infusion was significantly higher than that found at rest or at maximum exercise ($P < 0.01$).

ECG tracings recorded during the 150-min infusion test showed that 6 out of the 35 patients studied developed abnormalities. Two subjects displayed nodal rhythm, one during both tests and one only once. This rhythm developed when heart rates dropped to the 33–37 beats/min range. Another subject had nodal premature beats at a heart rate of 56–60 beats/min during his first infusion test but not during his repeat test after an exercise program. One other subject developed first degree atrial ventricular (AV) block (HR = 63–67 beats/min) on his baseline test. No final infusion study was performed on this subject. Another subject had a Mobitz type I second degree AV block (HR = 50–58 beats/min), which occurred during both tests between 130–150 min. A final subject developed an idioventricular rhythm with a rate of 49 beats/min. The test was immediately terminated. Except for the second degree AV block, all arrhythmias developed within 5 min of commencing the infusion; and every abnormality promptly disappeared with termination of the drug infusion. All patients displayed pallor and complained of coldness in their extremities during the propranolol, epinephrine, glucose, and insulin infusion and all developed vasodilation and displayed facial flushing after test completion. Several subjects reported a transient slight chest tightness during the initial 3–10 min of the test that did not occur throughout the remainder of the test. No other side effects were noted.

Thirty-five patients exercised to maximum tolerance on a treadmill 1 wk before the first infusion. Three abnormal S-T responses were noted; 5 patients developed ventricular premature beats; 2 had nodal premature beats during the exercise test. The exercise tests were repeated in 33 patients before the second infusion. Three of these had abnormal S-T responses, 2 of whom had abnormal S-T changes during the first test.

Results of maximal treadmill exercise testing did not predict which subjects would subsequently develop arrhythmias during the infusion test. One patient having nodal premature beats during the infusion had three isolated ventricular premature beats during maximum treadmill exercise. The patient with the idioventricular rhythm during infusion also displayed arrhythmias (6 simple premature ventricular beats) and an abnormal S-T segment response, but no angina with exercise. The remaining patients with infusion-related AV conduction abnormalities or with nodal rhythms had normal exercise ECGs.

DISCUSSION

Considerable evidence has accumulated to support the contention that insulin resistance is a major factor contributing to glucose intolerance of some patients with type II, non-insulin-dependent diabetes mellitus.[1,3,9–12] These findings have stimulated investigators to develop improved methods for assessing in vivo insulin resistance in man.[2–7] The technique originally described by Shen et al.[3] has been used in several investigations[13–17] as a means of assessing in vivo insulin resistance in persons with or without diabetes. No serious clinical complications have been reported but, except for the negative observations in the initial description of the method,[3] reports of cardiovascular monitoring have not been included. Kram et al.[18] have reported a marked sinus bradycardia and AV block in a 22-yr-old man given epinephrine in the presence of propranolol. This response was attributed to unopposed vagal activity. The elevated blood pressures in our patients would be expected to increase vagal tone through the mechanism of stimulating the baroreceptors. In the presence of beta blockade by propranolol, this effect would be further enhanced.

TABLE 1
Cardiovascular response to insulin resistance test and to maximal exercise texts ($\bar{x} \pm SD$)

	Rest values	Insulin resistance test*	Maximal exercise test
Heat rate (beats/min)	69.5 ± 9.59	51.0 ± 7.42†‡	179.0 ± 16.90†
Systolic blood pressure (mm Hg)	121.6 ± 13.85	148.8 ± 16.96†‡	195.0 ± 28.14†
Diastolic blood pressure (mm Hg)	78.2 ± 8.45	92.1 ± 7.91†‡	76.0 ± 17.68

* A mean value was obtained for each subject based on the 7 values taken at 10-min intervals from 90–150 min of the standard propranolol, epinephrine, glucose, and insulin infusion test (see MATERIALS AND METHODS).
† Significantly different from resting value, $P < 0.01$.
‡ Significantly different from maximum exercise value, $P < 0.01$.

Our observations suggest that potentially serious cardiac arrhythmias can develop during the 150-min propranolol, epinephrine, glucose, and insulin infusion. In our otherwise healthy but hyperlipidemic and/or mildly diabetic group of 35 middle-aged males, 17% of them had a documented arrhythmia during the infusion. Pallor and chest tightness were observed and marked bradycardia and hypertension were noted. Shen et al.,[3] in their initial description of the method, reported no abnormal ECG findings but stated that heart rates usually dropped 10–15 beats/min and that systolic blood pressures increased by an average of 20 mm HG (range 10–30 mm Hg). Similarly, our study documented a 19-beat/min reduction (range 8–31 beats/min) in heart rate, a 27-mm Hg increase (range 9–52 mm Hg) in systolic blood pressure, and a 14-mm Hg increase (range 5–32 mm Hg) in diastolic blood pressure. In contrast, however, cardiac arrhythmias were noted in 6 of our 35 subjects. In these 6 subjects showing arrhythmias during infusion, heart rates declined 17 beats/min (range 9–24 beats/min), systolic blood pressure rose 32 mm Hg (range 11–52 mm Hg), and diastolic blood pressure increased by 16 mm Hg (range 8–22 mm Hg).

All subjects had normal resting electrocardiograms; the absence of abnormalities on exercise testing did not preclude development of arrhythmias during the infusion test. The one patient with the onset of an idioventricular rhythm may have had coronary disease as evidenced by an abnormal S-T segment and ventricular premature beats during the exercise test. Possibly, patients having these findings should be excluded from infusion studies.

Our observations suggest that important but asymptomatic cardiac rhythm disturbances can develop during the infusion of propranolol, epinephrine, glucose, and insulin for measurement of in vivo insulin resistance. In view of these findings, we believe that alternative measures of insulin resistance should be considered in patients with abnormal electrocardiograms, particularly if sinus node dysfunction is present,[19] or with histories suggestive of coronary artery disease and that all subjects undergoing this test should have continuous cardiac monitoring. Finally, we would terminate the test promptly if second degree atrioventricular block, idioventricular rhythm, ventricular tachycardia, or other potentially serious rhythm disturbances were observed. If these arrhythmias do not readily revert after cessation of the infusion, then one should be prepared to treat with atropine.

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