ventricular asynergy in the prolapsing mitral leaflet syndrome. Am J Cardiol 29: 611, 1972

Efficacy of Propranolol in the Control of Exercise-Induced or Augmented Ventricular Ectopic Activity

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SUMMARY The effect of propranolol on exercise-induced or augmented ventricular ectopy was studied in sixteen male patients, six of whom had documented coronary artery disease. Fifteen patients were exercised after two weeks of oral therapy, fourteen after single oral therapy and eight patients after intravenous therapy. Propranolol dosage was titrated to produce maximal beta-adrenergic blockade.

Effective reduction of exercise-induced ventricular ectopy occurred in ten of fifteen patients (P < 0.001), and in five of six patients with coronary disease (P < 0.02). Propranolol therapy abolished ventricular couplets in eight of twelve patients and ventricular tachycardia in four of five patients. Single oral and intravenous therapy had similar or greater effects. Plasma propranolol levels following different routes of administration did not correlate with exercise-induced maximal heart rates or percent reduction in ventricular ectopy. When compared to exercise in eleven patients, ambulatory monitoring underestimated the severity, particularly the highest grades, of ventricular ectopy.

IT IS GENERALLY ACCEPTED that ventricular ectopic activity in the presence of ischemic heart disease requires therapeutic control because of its association with a high incidence of sudden cardiac death. However, the selection of a suitable antiarrhythmic agent has become a cause of much concern for reasons of either demonstrated inefficacy or a higher than acceptable incidence of therapeutic side effects. Furthermore, methods for the detection of ventricular ectopic activity have come under close scrutiny recently. The suggestion that both stress testing and prolonged ambulatory monitoring are necessary, not only for the demonstration of ventricular ectopic activity but also for the evaluation of the efficacy of antiarrhythmic therapy, requires further confirmation.

Although propranolol is known to be effective in the control of ventricular ectopic activity at rest, and the plasma levels required for the suppression of ventricular ectopic activity observed at rest have been documented, only individual cases of the utilization of propranolol in exercise-induced ventricular ectopic activity have been reported. The purpose of this study was to determine the effect of propranolol on exercise-induced or augmented ventricular ectopic activity, and to compare the plasma propranolol levels required for the suppression of ectopic activity during exercise with those previously reported to be effective in patients at rest. The relative value of brief periods of continuous ambulatory monitoring were compared with stress testing as a means of evaluating ventricular ectopic activity in patients before and after the administration of propranolol.
Materials and Methods

Patient Selection

Patients were selected from the male population of a Veterans Administration Hospital who were referred to the Cardiovascular Service for the evaluation of palpitations or ventricular premature beats. Patients were screened by history and physical examination, in addition to a routine 12-lead electrocardiogram and an upright chest roentgenogram. Patients with a history or clinical features of myocardial infarction within the previous six months, congestive cardiac failure, peripheral vascular disease, diabetes mellitus and asthma were excluded. If patients were taking antiarrhythmic therapy, these drugs were discontinued prior to study.

Criteria for admission to the study were a) a resting electrocardiogram without ventricular ectopic activity and exercise-induced ventricular premature beats at a rate of 3/min or greater, or b) ventricular premature beats at rest at a rate of 2/min or greater which failed to suppress or which increased in frequency during exercise. These criteria had to be met during two control multistage stress tests prior to the commencement of the study and during a final post-therapy control study performed 48 to 96 hours after the final administration of propranolol.

Sixteen male volunteers, whose ages ranged from 37 to 60 (mean 53 years), were studied. Six patients had a diagnosis of coronary artery disease, based on one or more of the following criteria: a) previous hospital admission for acute myocardial infarction, b) electrocardiographic evidence of a previous myocardial infarction, c) a classical pattern of angina pectoris with a positive stress test, or d) a 50% or greater stenosis of at least one coronary artery identified by cardiac catheterization. Ventricular ectopic activity was the only identifiable cardiac abnormality in 10 patients; five of these patients had experienced syncope on at least one occasion.

Details of the study were explained to each patient and informed, written consent was obtained.

Exercise Testing

Multistage ergometric exercise was performed using a Monark bicycle ergometer. The electrocardiogram was continuously monitored on a Hewlett Packard 1516A tape terminal attached to a Hewlett Packard 1309A oscilloscope, using a modification of Frank's orthogonal lead system. Permanent recordings at 25 mm/sec were made before exercise, during the last 30 seconds of each level of exercise obtained, and during the first 30 seconds of each postexercise minute of observation (three minutes or until return to control ventricular ectopic activity status). In addition, continuous 5 mm/sec recordings were obtained with a Marquette series 330 automatic strip chart recorder as a back-up to the visual monitoring routine. Indirect blood pressure recordings were obtained at one minute intervals throughout the study by the Doppler technique, utilizing an Arteriosonde (Roche).

Fifteen patients performed leg exercise. The protocol for continuous leg exercise used in this laboratory has been reported elsewhere.\textsuperscript{23, 24} End points of exercise in this laboratory are typical angina pectoris, electrocardiographic ST-segment changes of 1 mm or greater, hypotension or leg fatigue. The exercise protocol was modified so that the end point would be reached after nine minutes of exercise. In patients without prior exercise study, leg exercise was commenced at 150 Kpm, increasing by increments of 150 Kpm every three minutes, until the individual end point was reached. In patients who had a previous exercise study, leg exercise was commenced at a level such that, with increasing increments of 150 Kpm, the predetermined end point was reached after nine minutes of exercise. Leg exercise was continuous throughout the study. One patient performed arm exercise. The protocol for arm exercise used in this study has been reported previously.\textsuperscript{24}

Therapy

The dosage of propranolol was adjusted to produce maximal beta-adrenergic blockade. This was confirmed by a greater than 20% reduction in heart rate at maximal equivalent workloads during exercise, as previously reported.\textsuperscript{25} Test doses were given intravenously (10 mg) or as a single oral dose (40 mg) and the existence of maximal beta-adrenergic blockade was assessed by exercise heart rate response. Optimal times for exercise, as previously reported, were 30 minutes after intravenous or 2 hours after single oral administration.\textsuperscript{25} If maximal beta-adrenergic blockade was not achieved, the test dose was doubled and exercise repeated. If respective intravenous or single oral doses were 10 mg or 40 mg, chronic oral therapy was commenced at 40 mg QID (11 patients), if 20 mg or 80 mg, chronic therapy was 80 mg QID (three patients), and if 120 mg (oral), chronic therapy was 120 mg QID (one patient).

Samples were drawn to obtain plasma propranolol levels at times of optimal effect after different routes of administration. Plasma levels were measured by the Ayerst Laboratories, by the spectrophotometric method of Shand et al., without prior knowledge of the patient or dosage schedule.\textsuperscript{25}

Fifteen patients were exercised after at least two weeks of chronic oral administration of propranolol. Fourteen patients were exercised after a single oral dose and eight patients after an intravenous dose.

Ventricular Ectopic Activity

For each minute of control, exercise and postexercise recovery periods, ventricular premature beats were counted and graded. The criteria used for grading the ventricular ectopic beats (VPBs) were: 0 = absence of VPBs; 1 = isolated unifocal VPBs, rate less than 3/min; 2 = isolated unifocal VPBs, rate greater than 3/min; 3 = multiform VPBs; 4A = couplets (i.e., two consecutive VPBs); 4B = runs of 3 or more VPBs.\textsuperscript{12}

The number and grade of ventricular premature beats recorded for each exercise test during both the control and treatment periods was the highest number and grade seen during any minute of the test, including the postexercise period.

Ambulatory Monitoring

In 12 of the 16 patients, ambulatory monitoring for periods of four to eight hours were obtained using a single
channel model 400 Avionics recorder. Analysis of the recordings was performed with a model 650 Avionics Electrocadios scanner. Ventricular ectopic activity was counted and graded as recommended by Lown and Wolf.1

Statistical Analysis
Comparative data were analyzed by student and group t-tests to obtain probability values.

Results
Exercise Tests
Table 1 compares the results of control maximal exercise tests with the results of exercise tests performed during all modalities of propanolol therapy. At maximal equivalent workloads (control, 456 ± 35 Kpm; treated, 463 ± 38 Kpm), the mean heart rate was reduced by 21% (131 ± 2 beats/min to 104 ± 1 beat/min; P < 0.05) and the double product (heart rate × systolic blood pressure/100) by 37% (242 ± 12 to 153 ± 10; P < 0.001). The change in maximal oxygen uptake from 17.9 ± 0.5 to 17.3 ± 0.5 ml/kg/min was not statistically significant.

Ventricular Ectopic Activity
The reduction in the maximum number of ventricular premature beats (VPBs) seen during all modalities of therapy is shown in table 2, and the effect of therapy in patients with and without documented coronary artery disease is compared in figure 1. In all patients, there was a reduction from 30 ± 4 to 13 ± 4 VPBs per minute (P < 0.001). In 11 of 16 patients (69%), the reduction was greater than 60% (26 ± 3 to 5 ± 1 VPBs per minute) and five patients (31%) showed a reduction to grade 1 activity (less than 3 VPBs per minute). In one patient, ventricular ectopic activity was abolished completely. In the six patients with coronary artery disease, there was a significant reduction in the maximum number of VPBs from 22 ± 3 to 7 ± 5 VPBs per minute (P < 0.02). Five of the six patients (83%) showed a greater than 60% reduction (21 ± 3 to 2 ± 1 VPBs per minute) and four patients (67%) showed a reduction to grade 1 activity (less than 3 VPBs per minute). The sixth patient who did not show a greater than 60% reduction in VPBs underwent arm exercise. In the 10 patients without documented coronary artery disease, the maximum number of VPBs was reduced from 36 ± 6 to 16 ± 5 per minute (P < 0.001). Six of the 10 patients (60%) showed a greater than 60% reduction (31 ± 5 to 8 ± 2 VPBs per minute) and one patient showed a reduction to grade 1 activity (less than 3 VPBs per minute).

Table 1. Results in Exercise Tests in Control and Treatment Periods

<table>
<thead>
<tr>
<th>Workload (Kpm)</th>
<th>Control*</th>
<th>Treated*</th>
<th>Percentage change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>456 ± 13</td>
<td>463 ± 38</td>
<td>+1.5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>131 ± 2</td>
<td>104 ± 1</td>
<td>-21.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rate-pressure product†</td>
<td>242 ± 12</td>
<td>153 ± 10</td>
<td>-37.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MVO₂ (ml/kg/min)</td>
<td>17.9 ± 0.5</td>
<td>17.3 ± 0.5</td>
<td>-4.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean values ± standard error of mean.
†(Heart rate × systolic blood pressure)/100.
Abbreviations: Kpm = Kilometers per minute; MVO₂ = maximal oxygen uptake in milliliters per kilogram per minute; NS = not significant.

Table 2. Ventricular Ectopic Activity in Control and Treatment Studies*

<table>
<thead>
<tr>
<th>All patients</th>
<th>Control†</th>
<th>Treated†</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60% reduction</td>
<td>16</td>
<td>30 ± 4</td>
<td>13 ± 4</td>
</tr>
<tr>
<td>Reduction to grade 1 activity†</td>
<td>11</td>
<td>26 ± 3</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Patients with documented coronary artery disease</td>
<td>5</td>
<td>18 ± 3</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>&gt; 60% reduction</td>
<td>6</td>
<td>22 ± 3</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Reduction to grade 1 activity</td>
<td>5</td>
<td>21 ± 3</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Patients without documented coronary artery disease</td>
<td>4</td>
<td>19 ± 3</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>&gt; 60% reduction</td>
<td>10</td>
<td>36 ± 6</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>Reduction to grade 1 activity</td>
<td>6</td>
<td>31 ± 5</td>
<td>8 ± 2</td>
</tr>
</tbody>
</table>

*The values represent the maximum number of ventricular premature beats seen during any minute of exercise including the post-exercise period.
†Mean values ± SEM.
‡Grade 1 activity refers to isolated, unifocal ventricular premature beats of less than 3/min.
minute ($P < 0.001$). In all eight patients (100%), this represented a greater than 60% reduction and six of the eight patients (75%) showed a reduction to grade 1 activity.

Several patients had higher grades of ventricular ectopic activity recorded during control exercise tests when compared to tests performed during therapy. Grade 4A activity (ventricular couplets), seen in 12 patients during control tests, was present in four patients (33%) after therapy. Four of the 12 patients had coronary artery disease, and grade 4A activity persisted in one after therapy. This patient underwent arm exercise. Exercise induced grade 4B activity (runs of 3 or more VPBs) was seen during control test in five patients and persisted in one patient after therapy. None of these patients had coronary artery disease.

Eleven of the 15 patients on chronic oral propranolol therapy had ambulatory monitoring recordings for 4 to 8 hours during control and treatment periods. Figure 3 compares the effect of therapy on different grades of ventricular ectopic activity detected by exercise testing and 4 to 8 hours of ambulatory monitoring. Ventricular ectopic activity, recorded in all patients during the control period during both exercise and ambulatory monitoring, was recorded during the treatment period in all patients (100%) during exercise and in seven of the 11 patients (64%) during ambulatory monitoring.

The detection of higher grades of ventricular ectopic activity by the two methods is also shown in figure 3. Ventricular couplets (grade 4A activity) recorded during exercise were seen in seven of 11 patients (64%) during the control period and in one patient during treatment; ambulatory monitoring detected grade 4A activity in one patient during the control period and in no patients during the treatment period. Runs of three or more VPBs (grade 4B activity) were recorded during exercise in three of these 11 patients (27%) but were not recorded by ambulatory monitoring during the control period. Grade 4B activity was not detected by either exercise or ambulatory monitoring during the treatment period.

Five patients, none of whom had documented coronary artery disease, had experienced syncope on at least one recent occasion. Four of the patients had ambulatory monitoring. Figure 4 compares the effect of propranolol therapy on

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**Table 3. Ventricular Ectopic Activity after Different Routes of Propranolol Administration**

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Control†</th>
<th>Treated‡</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic oral therapy</td>
<td>15</td>
<td>30 ± 5</td>
<td>13 ± 4</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>&gt; 60% reduction</td>
<td>10</td>
<td>26 ± 4</td>
<td>5 ± 2</td>
<td></td>
</tr>
<tr>
<td>Reduction to grade 1 VEA</td>
<td>5</td>
<td>18 ± 3</td>
<td>1 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Single oral therapy</td>
<td>14</td>
<td>31 ± 5</td>
<td>7 ± 3</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>&gt; 60% reduction</td>
<td>12</td>
<td>39 ± 5</td>
<td>3 ± 2</td>
<td></td>
</tr>
<tr>
<td>Reduction to grade 1 VEA</td>
<td>10</td>
<td>25 ± 4</td>
<td>1 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Intravenous therapy</td>
<td>8</td>
<td>36 ± 7</td>
<td>4 ± 3</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>&gt; 60% reduction</td>
<td>8</td>
<td>38 ± 7</td>
<td>4 ± 3</td>
<td></td>
</tr>
<tr>
<td>Reduction to grade 1 VEA</td>
<td>6</td>
<td>30 ± 5</td>
<td>1 ± 0.5</td>
<td></td>
</tr>
</tbody>
</table>

*The values represent the maximum number of ventricular premature beats seen during any minute of exercise including the post-exercise period.
†Mean values ± sem.
different grades of ventricular ectopic activity seen in these patients. Grade 4A activity, recorded in four of the patients (80%) during control exercise tests, was seen in only one patient during the treatment period. Grade 4B activity, observed in three patients (60%) during control tests, was seen in one patient during therapy.

Ambulatory monitoring which recorded some degree of ventricular ectopic activity in all four patients during the control period and in two patients (50%) during therapy, detected grade 4A activity in only one patient during the control period and did not record grade 4B activity in any of these four patients. Grade 4A or 4B activity was not detected during the treatment period of ambulatory monitoring.

Plasma Propranolol Levels

Table 4 compares the plasma propranolol levels after different routes of administration with the dosage of propranolol and the percent reduction in exercise-induced or augmented ventricular ectopic activity. Mean plasma propranolol levels in patients on chronic oral therapy were 85 ± 14 ng/ml in 11 patients on 160 mg daily, 148 ± 53 ng/ml in three patients on 320 mg daily and 322 ng/ml in one patient on 480 mg daily. The range of values for patients on chronic therapy was 40–322 ng/ml. In patients studied after single oral therapy, mean plasma propranolol levels were 39 ± 7 ng/ml in seven patients after a 40 mg dose, 97 ± 15 ng/ml in three patients after an 80 mg dose and 170 ng/ml in one patient after a 120 mg dose. The range of values for these patients was 26–170 ng/ml. In patients studied after intravenous administration, mean plasma propranolol levels were 125 ng/ml in one patient after 10 mg dose and 58 ± 11 ng/ml in five patients after a 20 mg dose. The range of values for these patients was 25–125 ng/ml.

No correlation was found between plasma propranolol levels and the percentage reduction in exercise-induced or augmented ventricular ectopic activity in patients on chronic therapy (r = 0.2), after single oral dosage (r = 0.1) or after intravenous administration (r = 0.7). When plasma
Table 4. Percentage Reduction of Exercise-Induced or Augmented Ventricular Ectopic Activity in Individual Patients Compared to Dose of Propranolol, Route of Administration and Plasma Propranolol Level

<table>
<thead>
<tr>
<th>Patient</th>
<th>Chronic therapy</th>
<th>Single oral therapy</th>
<th>Intravenous therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily dose (mg)</td>
<td>Plasma level (ng/ml)</td>
<td>Percent reduction in VEA*</td>
</tr>
<tr>
<td>1</td>
<td>480</td>
<td>322</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>160</td>
<td>101</td>
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<td>80</td>
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<td>60</td>
</tr>
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<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>320</td>
<td>111</td>
<td>52</td>
</tr>
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<td>11</td>
<td>160</td>
<td>104</td>
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</tr>
<tr>
<td>12</td>
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<td>116</td>
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<td>320</td>
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<td>40</td>
<td>63</td>
</tr>
<tr>
<td>15</td>
<td>320</td>
<td>82</td>
<td>28</td>
</tr>
<tr>
<td>16</td>
<td>160</td>
<td>—</td>
<td>78</td>
</tr>
</tbody>
</table>

*VEA = Maximum number of ventricular premature beats seen during any minute of exercise including the postexercise period.

Propranolol levels were compared to maximal exercise-induced heart rates following the different routes of administration of propranolol, no correlation was found in patients on chronic therapy ($r = 0$), after single oral dosage ($r = 0$) or after intravenous administration ($r = 0.7$).

Toxic Effects

Propranolol was well tolerated by all patients and no side effects of the drug were reported in the dosage schedules administered during the study.

Discussion

The management of ventricular ectopic activity is not only controversial but also a subject of much concern to the clinician for several reasons. Because of its epidemiological association with a high incidence of sudden cardiac death, the occurrence of grade 2 or higher ventricular ectopic activity in patients with ischemic heart disease probably warrants therapeutic control.1 However, several studies of antiarrhythmic agents have reported their inefficacy or frequency of significant side effects.6, 7, 18, 27, 28

The optimal method of detection of ventricular ectopic activity has also been a subject of discussion, and both twelve and twenty-four hour ambulatory monitoring and stress testing are considered superior to resting electrocardiograms for the detection of ventricular ectopic activity and the demonstration of efficacy of antiarrhythmic therapy.14-19 In this laboratory, the combination of stress testing and four hour ambulatory monitoring was more sensitive in the detection of ventricular ectopic activity than either method separately in a group of 50 postmyocardial infarction patients.29

Propranolol is reported to be effective in the management of ventricular ectopic activity at rest.26 However, little is known concerning its efficacy in exercise-induced or augmented ventricular ectopic activity. It would seem that exercise testing would be doubly useful in evaluating its effects because such testing can also demonstrate whether maximal beta-adrenergic blockade is present.29

The results of this study show that propranolol was effective in the suppression of exercise-induced or augmented ventricular ectopic activity and the degree of suppression was greater than 60% in more than two-thirds of the patients studied irrespective of the route of administration. Furthermore, propranolol was most effective in suppressing ventricular couplets (in 67% of patients) and ventricular tachycardia (in 80% of patients). Although the selection of 60% reduction is arbitrary, others have considered 50% or greater to be an effective antiarrhythmic response.30 Suppression of ventricular ectopic activity was particularly impressive in the patients with coronary artery disease. Grade 4A activity persisted in only one patient after therapy. This was the only patient who underwent arm exercise, raising the question of whether the cardiovascular response to arm exercise differs from the response to leg exercise.

In the five patients who gave a recent history of syncope, four had grade 4A ventricular ectopic activity and three had grade 4B activity. Although the etiology of the syncope in these patients was not known, it is possible that the syncopal episodes were due to a high grade paroxysmal arrhythmia, such as ventricular tachycardia. If this was the case, then the effectiveness of propranolol in suppressing the highest grades of ventricular ectopic activity, as demonstrated in this study, would indicate its value in these patients.

In this study, short periods of 4 to 8 hours of ambulatory monitoring were less sensitive than exercise in detecting ventricular ectopic activity, which concurs with two recent reports that only with longer periods of monitoring does this technique prove more sensitive.18, 19 Furthermore, ambulatory monitoring proved less sensitive in the detection of grades 4A and 4B ventricular ectopic activity. Ryan and his associates have previously reported the limitations of ambulatory monitoring in detecting the highest grades of ventricular ectopic activity, and have postulated that exercise and ambulatory monitoring may be complimentary methods of determining different information regarding the electrophysiological state of the myocardium.19

The range of plasma propranolol levels obtained during any route of administration of propranolol was widespread, the total range being from 25 to 322 ng/ml. Colart et al. have previously reported that, following the intravenous ad-
ministration of racemic propranolol to twelve patients, ventricular premature beats recorded at rest were completely suppressed at lower plasma propranolol levels (range 40 to 85 ng/ml) than levels obtained when complete suppression did not occur (range 70 to 200 ng/ml).28 However, there was some overlap of plasma levels even in their small group of patients. In this study following intravenous propranolol administration, exercise-induced or augmented ventricular ectopic activity was effectively suppressed in all eight patients and abolished in four of these patients, whose plasma propranolol levels ranged from 67 to 125 ng/ml.

A study by Pine et al. of the correlation of plasma propranolol concentration with the therapeutic response in patients with angina pectoris reported wide variation in both chronic oral dose and plasma propranolol levels.29 The plasma levels obtained in this study fall in the same wide range as those reported by Pine et al., for both exercise-induced ventricular ectopy suppressed patients and those not suppressed, all of whom had maximal beta-adrenergic blockade confirmed by appropriate exercise-induced heart rate response reduction. Thus, in these patients, effective suppression of exercise-induced or augmented ventricular ectopic activity could not be linearly correlated with plasma propranolol levels. All plasma levels, however, fell within or above the range associated with individual maximal therapeutic benefit and above the ED₉₀ level of chronotrophic beta-adrenergic blocking activity as defined by Pine and his colleagues.29

The hemodynamic changes after maximal beta-adrenergic blockade are well known.30 Although it has a direct depressant action on myocardial contractility, the overall effect of propranolol during exercise is to lower cardiac work by reducing the heart rate and systemic blood pressure response. If ventricular ectopic activity is due to myocardial ischemia and/or catecholamine release, then the reduction in myocardial oxygen demand and protection against catecholamine-induced irritability produced by propranolol during exercise would be expected to reduce the frequency of ventricular ectopic activity, as was shown in this study.

The greater effectiveness of intravenous and single oral dosage of propranolol in suppressing exercise-induced or augmented ventricular ectopy when compared to chronic oral therapy was difficult to explain. Exercise was carried out at the recommended times after individual therapeutic administration, ruling out the possibility that beta blockade did not exist at the time of study.28 If a training effect had caused a better performance in patients on chronic oral therapy, one would have expected an increase in maximal workload during the treatment period, which did not occur. The development of drug tolerance was a possibility that could not be confirmed.

Finally, there remained the possibility that the reduction in exercise-induced or augmented ventricular ectopic activity observed during the periods of therapy may have been related to a placebo effect. The short periods of therapy, combined with the reproducibility of ventricular ectopy during three control tests necessary for admission to the study did not rule out biofeedback conditioning or other placebo effects completely, but served to make them unlikely.

Several conclusions may be drawn from this study. Maximal stress testing was useful in assessing both the efficacy of propranolol as an antiarrhythmic agent and in indicating the presence of maximum beta-adrenergic blockade. Propranolol was effective in the suppression of exercise-induced or augmented ventricular ectopic activity, and particularly effective in the suppression of the highest grades of ventricular ectopic activity, i.e., ventricular couplets and ventricular tachycardia. Suppression of ventricular ectopy was most pronounced in the patients with documented coronary artery disease. Short periods of ambulatory monitoring proved less sensitive than exercise in determining the efficacy of propranolol, particularly with respect to the highest grades of ventricular ectopic activity, suggesting that both exercise and long periods of ambulatory monitoring are required to determine the effectiveness of antiarrhythmic therapy.

Acknowledgment

The authors wish to express their gratitude to Janet Park and Frankie Kirkwood for their technical assistance, and to Barbara Oxman, Toni Hooten and Pauline Mckee for their secretarial help.

References

Effect of Phasic Respiration on Left Ventricular Dimension and Performance in a Normal Population
An Echocardiographic Study

JOEL I. BRENNER, LCDR, MC, USNR, AND ROBERT A. WAUGH, CDR, MC, USNR

With the technical assistance of Roger D. Harsh, HMI, USN

SUMMARY Echocardiographic examination of the left ventricle (LV) in 30 normal subjects, 5 to 47 years of age, was performed in order to analyze the effects of phasic respiration on LV dimensions and derived LV function. Peak expiratory and peak inspiratory LV diastolic and systolic dimensions were measured and extrapolated to volume estimates using a standard formula. Although there was wide variation in the individual measurements, and particularly in systolic dimension, the mean peak inspiratory diastolic dimension, derived diastolic volume, and stroke volume all decreased significantly (P < 0.001); a smaller decrease in ejection fraction was seen (P < 0.02), while the changes in mean end-systolic dimension and end-systolic volume were not significant.

While these observed changes may reflect a true physiologic variation, an artificial component cannot be excluded. Regardless of their physiologic significance, however, these data show that the effect of phasic respiration is a factor to be considered in correlation echocardiographic studies of LV function in both normal and, possibly, pathologic cardiovascular conditions.

diovascular disease. Recent attention has been directed to the evaluation of LV volume alterations and, hence, LV function in normal subjects during various acute hemodynamic interventions and the effects of respiration on these same parameters in patients with pericardial effusion. We too have noted marked respiratory variation in the LV internal dimensions in some patients with pericardial effusion, but changes of a similar or even greater magnitude frequently were seen in patients with a normal cardiovascular system. The present study, therefore, was undertaken to quantitate the magnitude of change in echocardiographic LV dimensions and derived function during the respiratory cycle in a group of normal subjects and thereby to provide a frame of reference for the interpretation of these changes in patients with cardiorespiratory pathology.

Methods
A final group of 30 subjects, ranging in age from 5 to 47 years, with a mean age of 20 years, was accepted for evaluation. There was no evidence for cardiopulmonary disease or hypertension in any subject. Echocardiographic evaluation

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The opinions and assertions expressed are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department.
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Received November 26, 1976; revision accepted August 8, 1977.
Efficacy of propranolol in the control of exercise-induced or augmented ventricular ectopic activity.
J V Nixon, W Pennington, W Ritter and W Shapiro

Circulation. 1978;57:115-122
doi: 10.1161/01.CIR.57.1.115

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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