Evaluation of Metoprolol in Suppressing Complex Ventricular Arrhythmias

CRAIG M. PRATT, MD, SHEILA C. YEPSEN, RN, CVNS, M. G. KIM BLOOM, MD, ADDISON A. TAYLOR, MD, JAMES B. YOUNG, MD, and MIGUEL A. QUINONES, MD

This study documents the extent of suppression of premature ventricular beats which can be achieved with metoprolol, a semiselective beta-adrenergic blocking agent, at doses of 100 to 200 mg daily, utilizing a single-blind placebo-controlled 10-day protocol with continuous ambulatory electrocardiographic recording of 20 patients with cardiac disease and complex ventricular arrhythmias. Metoprolol (200 mg/day) resulted in suppression of 60% of total premature ventricular beats, with couplets (pairs) and ventricular tachycardia decreased 84% and 94%, respectively (all $p < 0.01$). Exercise-induced premature ventricular beats, especially ventricular tachycardia, were effectively suppressed. The peak plasma metoprolol level to achieve these results was 72 ± 34 ng/ml (mean ± 1 standard deviation). At this plasma concentration, the mean 24-hour heart rate during normal activity was reduced from 78 ± 8 beats/min (placebo) to 62 ± 4 (metoprolol 200 mg/day)($p < 0.001$). Beta blockade also was demonstrated by a 20% reduction in heart rate during maximal Bruce exercise testing with metoprolol 200 mg/day. Although resting left ventricular function was not affected by metoprolol, pulmonary function tests show a statistically significant decrease in forced vital capacity, forced expiratory volume in 1 second, and forced expiratory flow rates (25-75) reversible with a beta-2 agonist.

Ventricular rhythm disturbances have prognostic significance in identifying an increased risk for sudden cardiac death in patients after myocardial infarction.[1,2] Beta-adrenergic blocking agents are efficacious in suppressing ventricular arrhythmias, especially in specific clinical settings including catecholamine excess, digitalis toxicity, mitral valve prolapse, and those induced by exercise.[3-6] Importantly, in numerous prospective placebo-controlled randomized clinical trials of beta-blockers in patients after myocardial infarction, cardiac mortality and sudden cardiac death have been reduced. Propranolol, timolol, and metoprolol have achieved the most significant reduction in mortality and sudden death in these large clinical trials.[7-9] Although a reduction in mortality and sudden death has been documented, it has not been demonstrated that this reduction is due to suppression of ventricular arrhythmias.

Despite a substantial experience with beta-blockers, the ventricular antiarrhythmic efficacy of metoprolol is poorly documented. Since the semiselective properties of this beta-blocker may be beneficial to patients with asthma or obstructive lung disease, this study was designed to assess the effect of metoprolol in suppressing complex ventricular arrhythmias, with concomitant measurement of left ventricular function, pulmonary function, and correlation with plasma metoprolol levels.

Methods

The study population consisted of 20 patients (10 male, 10 female; mean age 57 ± 8 years) with screening 24-hour ambulatory electrocardiograms demonstrating complex ventricular rhythm disturbances (frequent premature ventricular beats [PVB] ≥30 per hour, couplets, ventricular tachycardia [VT]). All 20 patients had documented cardiac disease: 15

From the Section of Cardiology, Baylor College of Medicine and The Methodist Hospital, Houston, Texas. This study was supported in part by Grant HL-17269 from the National Heart, Lung, and Blood Vessel Research and Demonstration Center, Baylor College of Medicine, and Biomedical Research Support Grant P-14, General Clinical Research Center, The Methodist Hospital, Houston, Texas. Computational assistance was provided by the CLINFO Project funded by Grant RR-00350, Division of Research Resources, National Institutes of Health, Bethesda, Maryland. Manuscript received October 19, 1982; revised manuscript received March 21, 1983, accepted March 28, 1983.

Address for reprints: Craig M. Pratt, MD, Assistant Professor of Medicine, Section of Cardiology, Baylor College of Medicine, and The Methodist Hospital, 6565 Fannin, MS F1001, Houston, Texas 77030.

patients had coronary artery disease documented by previous myocardial infarction, coronary arteriography or both; 2 patients had hypertensive heart disease; 3 patients had cardiomyopathy. All antiarrhythmic medications except digitalis were discontinued at least 72 hours before the study.

The study design consisted of a 10-day placebo-controlled single-blind protocol (3 days of placebo, 3 days of metoprolol 25 mg orally 4 times a day, 4 days of metoprolol 50 mg orally 4 times a day) with continuous 24-hour ambulatory electrocardiographic recordings. These were recorded on the Avionics® 445 A 2-channel system (Irvine, California) and analysis was performed on an Avionics 668 scanner. Tapes were analyzed by 2 independent investigators. Test tapes in our laboratory show a reproducibility of 92, 93, and 95% for total counts of PVB, couplets, and VT, respectively.

Ventricular arrhythmias, as well as heart rates during normal activity, were quantitated hourly during the entire 10-day study. Symptom-limited exercise testing was performed with placebo and metoprolol (200 mg/day) utilizing the standard Bruce protocol with quantitation of ventricular arrhythmias during exercise and recovery periods. Two-dimensional echocardiographic assessment of left ventricular function was performed during placebo and metoprolol dosing on an ATL® (Bellville, Washington) mechanical sector scanner and the left ventricular ejection fraction was calculated by a method previously reported from this laboratory.[10] Sector scans performed during placebo dosing on at least 2 consecutive days demonstrated a reproducibility of the left ventricular ejection fraction of ±3%.

Pulmonary function testing was performed during placebo, then 3 times during metoprolol dosing (2 hours after the first 25 mg dose, day 3 of 25 mg 4 times daily, 2 hours after first 50 mg dose).

Spirometry was performed on an Ohio® 850 rolling-seal spirometer (Madisonville, Wisconsin) utilizing a Collins Eagle® microprocessor (Braintree, Massachusetts). Forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV_1) were selected from the best of ≥3 forced expiratory maneuvers. The mid-maximal expiratory flow rate (FEF [25-75]) was selected from the "curve" with the best total of FVC and FEV_1. Functional residual capacity and airway resistance were determined with an Ohio variable-pressure body plethysmograph. Total lung capacity was calculated from the functional residual capacity and the inspiratory capacity during a slow vital capacity maneuver. Spirometry and plethysmography were repeated 15 minutes after metaproterenol (1.5 mg) aerosolized inhalation. Data before and after bronchodilators were expressed from norms described by Morris,[11] Goldman,[12] Boren,[13] and their co-workers. Arterial blood gases were also obtained during placebo and metoprolol dosing.

Metoprolol plasma samples were obtained during placebo administration, and once during low- and high-dose metoprolol with samples obtained 2 hours after each dose. Additionally, a 5-hour postdose sample was taken during high-dose metoprolol therapy. All plasma samples were obtained after at least 5 doses of metoprolol at each dose range to insure a steady state at the sampling time. Quantitation of metoprolol in human plasma was performed by fluorometry after high-pressure liquid chromatographic separation. Pronethalol was used as an internal standard. Known amounts of metoprolol ranging from 5 to 1,000 ng/ml were added to plasma samples obtained from persons taking no drugs; these samples were analyzed concurrently with those from patients taking metoprolol. A standard curve for metoprolol was then constructed by linear regression plot of metoprolol/pronethalol peak height ratio versus drug concentration in the spiked samples. Metoprolol concentration in the sample patient plasma was then calculated from the regression line by the formula $Y = mx + b$, where Y is the peak height ratio, m is the slope of the regression line, x is the metoprolol concentration, and b is the Y-intercept. This method allows detection of as little as 10 ng/ml of metoprolol with intraassay and interassay coefficients of variation of 5.4% and 8.3%, respectively. Commonly used cardiovascular drugs do not interfere with this assay.

Statistical analysis was performed with the *t* statistic for paired data. The Wilcoxon signed ranks test was used for data that were not normally distributed.

TABLE I Premature Ventricular Beats (PVB): Placebo Versus Low- and High-Dose Metoprolol

Patient	3-Day Placebo: Mean PVB/24 hours	3-Day Metoprolol (100 mg/day): Mean PVB/24 hours	4-Day Metoprolol (200 mg/day): Mean PVB/24 hours
1	22,160	19,794	8,218
2	1,078	341	245
3	5,443	74	11
4	6,654	124	56
5	22,205	11,836	4,306
6	25,904	23,138	11,479
7	10,357	8,305	5,085
8	3,560	1,651	271
9	18,556	3,521	2,330
10	2,604	1,876	202
11	1,840	282	285
12	10,905	4,644	4,045
13	7,123	5,708	3,397
14	7,214	8,754	5,132
15	16,400	15,105	13,400
16	2,783	3,392	3,111
17	409	361	245
18	4,691	3,881	3,923
19	1,090	652	1,081
20	1,944	1,269	1,702
Mean	8,646	5,735	3,536
Standard deviation	±8,063	±6,824	±4,117
Standard error	1,803	1,526	920
Plasma metoprolol level	0	33 ng/ml (8.6–210)	72 ng/ml (17–178)
Standard deviation	0	22 ng/ml	34 ng/ml

* $p < 0.001$ versus placebo, $p < 0.02$ versus low-dose metoprolol.

Results

Efficacy of metoprolol in suppressing ventricular arrhythmias: During 3 days of placebo ambulatory electrocardiographic recording, the mean premature ventricular beat frequency was 8,640/24 hours (Table I). Three days of low-dose metoprolol (25 mg orally 4 times daily) resulted in a mean reduction of PVB to 5,735/24 hours ($p < 0.01$ versus placebo). After 4 days of ambulatory electrocardiographic recording with high-dose metoprolol (50 mg orally 4 times daily), the mean frequency of PVB was further reduced to 3,536/24 hours ($p < 0.001$ versus placebo, $p < 0.02$ versus low-dose metoprolol). Of the 20 patients, 13 had ≥50% reduction in total PVB, 8 had >70% reduction, and 4 patients had >90% reduction in PVB.

Quantitation of ventricular couplets (Table II) revealed a progressive decrease in mean couplet frequency with low- and high-dose metoprolol—a maximal 84% reduction—which was highly significant ($p < 0.002$). Analysis of the 10 patients with VT during placebo

TABLE II Ventricular Couplets: Placebo Versus Low- and High-Dose Metoprolol

Patient	3-Day Placebo: Mean Couplets/24 hours	3-Day Metoprolol (100 mg/day): Mean Couplets/24 hours	4-Day Metoprolol (200 mg/day): Mean Couplets/24 hours
1	104	1	3
2	8	6	1
3	46	1	1
4	18	18	6
5	39	152	1
6	713	49	50
7	1,700	965	333
8	7	1	0
9	2	0	0
10	71	7	2
11	228	2	4
12	11	9	18
13	39	9	23
14	6	3	0
15	3	1	4
Mean	200	81	30
Standard deviation	453	248	85
Standard error	117	64	22
p value versus placebo	0	<0.01*	<0.002*

* Wilcoxon signed ranks test.

ambulatory electrocardiographic recording (Table III) showed a 94% reduction during high-dose metoprolol therapy, with total abolition of VT in 6 of 10 patients ($p < 0.01$).

Ventricular arrhythmias during maximal Bruce exercise testing were analyzed in 13 patients with both placebo and metoprolol dosing. During the placebo test, 10 of 13 patients had PVB during exercise or in the recovery phase, 7 of 13 had couplets, and 3 of 13 had exercise-induced VT. With metoprolol, in addition to an overall 70% decrease in total PVB, there was total abolition of couplets in 5 of 7 patients and elimination of exercise-induced VT in all patients.

TABLE III Ventricular Tachycardia (VT): Placebo Versus Low- and High-Dose Metoprolol

Patient	3-Day Placebo: Mean VT Runs/24 hours	3-Day Metoprolol (100 mg/day): Mean VT Runs/24 hours	4-Day Metoprolol (200 mg/day): Mean VT Runs/24 hours
1	7	1	1
2	2	0	0
3	2	0	0
4	25	1	1
5	7	3	1
6	127	29	5
7	2	0	0
8	31	0	0
9	5	0	0
10	3	1	1
Mean	22.7	3.8	0.75
Standard deviation	40.6	9.5	1.8
Standard error	13.5	3.2	0.6
p value versus placebo	0	<0.01*	<0.01*

* Wilcoxon signed ranks test.

In addition to the demonstrated reduction in mean heart rate with metoprolol, the degree of beta blockade was further verified by a decrease in double product during maximal Bruce exercise testing from placebo (23,237 ± 5,368) to high-dose metoprolol (15,500 ± 3,548) despite comparable exercise duration (6.32 ± 1.81 minutes versus 6.88 ± 2.07 minutes, placebo versus metoprolol therapy, respectively; difference not significant).

Metoprolol plasma levels: During low doses of metoprolol (100 mg/day) peak mean plasma metoprolol levels 2 hours after a dose were 33 ± 22 ng/ml. Peak mean plasma metoprolol levels at 200 mg/day dosage were 72 ± 34 ng/ml. Trough mean plasma metoprolol levels (5 hours after dosing) during high-dose metoprolol were 41 ± 45 ng/ml.

Mean heart rate for each 24 hours was quantitated over the 10-day period with continuous ambulatory electrocardiographic recording. There was a highly significant ($p < 0.001$) incremental decrease in the mean heart rate from placebo (78 ± 8 beats/min) to low-dose metoprolol (72 ± 6 beats/min, mean peak plasma metoprolol level 33 ± 22 ng/ml) and high-dose metoprolol (62 ± 4 beats/min, mean plasma metoprolol level 72 ± 34 ng/ml).

The peak plasma metoprolol level achieved during steady-state dosing in each patient during high-dose therapy is seen in Figure 1. There was no relation to this plasma level and the percent reduction of PVB on that day of ambulatory electrocardiographic recording ($p < 0.12$).

The relation between the mean heart rate during the hour each plasma metoprolol level was obtained (both peak and trough levels) is seen in Figure 2. There was a statistically significant correlation between plasma metoprolol concentration and the mean heart rate for the specific hours sampled ($r = 0.41$, $p < 0.001$).

Relationship of metoprolol therapy to ventricular function: Two-dimensional echocardiograms performed during placebo dosing demonstrated a mean resting left ventricular ejection fraction of 50 ± 10%

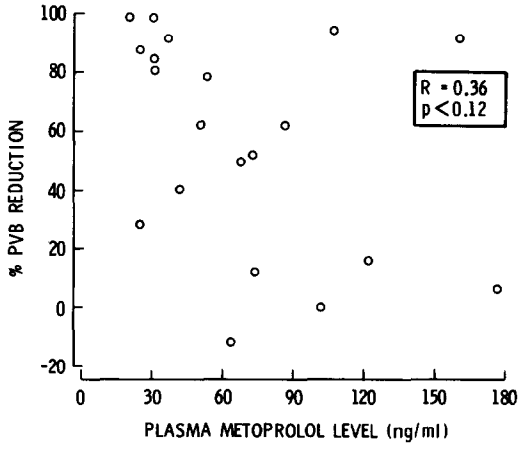

FIGURE 1. Relation of premature ventricular beat (PVB) reduction to maximal plasma metoprolol level achieved.

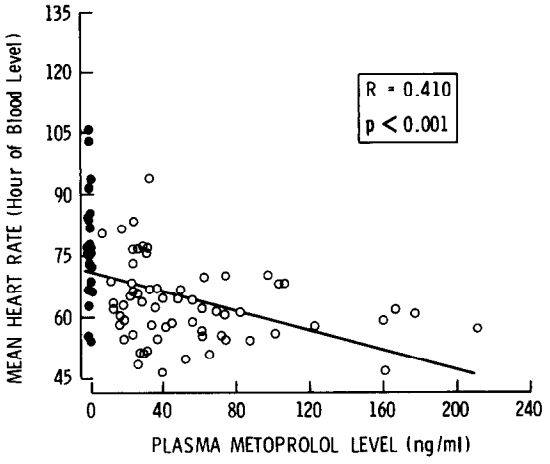

FIGURE 2. Mean heart rate during normal activity relative to metoprolol plasma concentration. **Closed circles,** placebo; **open circles,** metoprolol.

(range 22 to 71). There was no statistical difference in the ejection fraction with 200 mg/day of metoprolol (mean 48 ± 9.2%, range 31 to 68). No patient required discontinuation from the study because of clinical congestive heart failure; however, 1 patient did require increasing diuretic therapy while taking metoprolol (placebo ejection fraction of 32%, unchanged with metoprolol). Of the 4 patients with resting left ventricular ejections <40% with placebo, none had a further decrease in ejection fraction while taking metoprolol.

Relationship of metoprolol therapy to pulmonary function: Baseline pulmonary functions obtained in 18 patients during the placebo period revealed normal ventilatory function in 6, a mild restrictive defect in 4 (total lung capacity 80 to 90% predicted with normal FEV_1/FVC ratios), and obstructive airways disease in 8 (5 with FEF [25-75] <60% and normal FEV_1/FVC ratios, and 3 with FEF [25-75] <60% and reduced FEV_1/FVC ratios).

The mean FEV_1 during placebo therapy expressed as a percentage of predicted value was 89 ± 21%. After the first dose of 25 mg of metoprolol, the mean FEV_1 decreased to 85 ± 20% of predicted ($p < 0.013$). After 3 days of low-dose therapy, there was a further decrease in mean FEV_1 to 80 ± 23% of predicted ($p < 0.005$). After the first dose of 50 mg of metoprolol, this decrease was sustained; the mean FEV_1 was 81.5 ± 21% ($p < 0.001$) (Fig. 3).

The FVC and FEF (25 to 75) followed similar patterns. During placebo therapy, the mean FVC was 86 ± 11% of predicted, which decreased to 82 ± 14% with low-dose metoprolol, and to 80 ± 15% of predicted during the high-dose regimen ($p < 0.05$). The FEF (25 to 75) was 67 ± 38.5% before and 55 ± 29% after the first dose of metoprolol ($p < 0.037$), with no decrease during further dosing.

The changes in functional residual capacity, FEV_1, and FEF (25-75) induced by metoprolol were obliterated by the administration of aerosolized metaproterenol (Fig. 4). There were no differences in the groups when peak expiratory flow rates, airway resistance, specific conductance, thoracic gas volume, and total lung capacity were analyzed and compared. Arterial blood gases were unaffected by metoprolol therapy.

Despite the documented deterioration of FVC, FEV_1, and FEF (25-75), only 1 patient had clinically apparent deterioration of chronic airway obstruction (baseline FEV_1 33% of predicted) which required a decrease in metoprolol dosing to 100 mg/day and supplemental bronchodilator therapy.

Discussion

This study provides previously unavailable continuous ambulatory electrocardiographic monitoring data which document the efficacy of metoprolol in suppressing ventricular arrhythmias, and thus allow comparison to data available on other beta-blockers. Coltart et al[14,15] documented "significant" suppression of PVB at a plasma propranolol level of 40 to 85 ng/ml, a level which was also associated with significant beta blockade. Winkle et al[5] demonstrated at least a 75% reduction in PVB in 5 of 9 patients with mitral valve prolapse who were taking propranolol doses of 160 mg/day. Woosley et al[16] demonstrated a 70% suppression of PVB at a

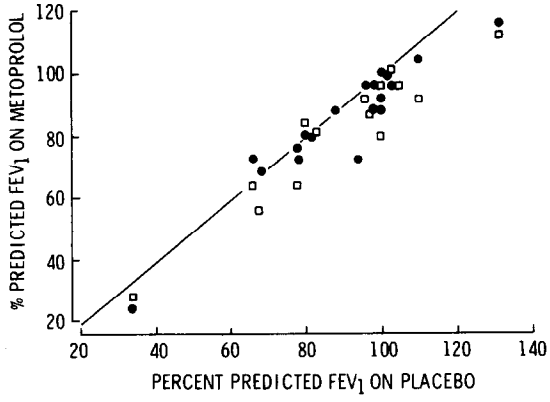

FIGURE 3. Percent change in FEV_1, placebo versus metoprolol before metaproterenol. FEV_1 = forced expiratory volume in 1 second. **Closed circles,** metoprolol, 100 mg/day; **open squares,** metoprolol, 200 mg/day.

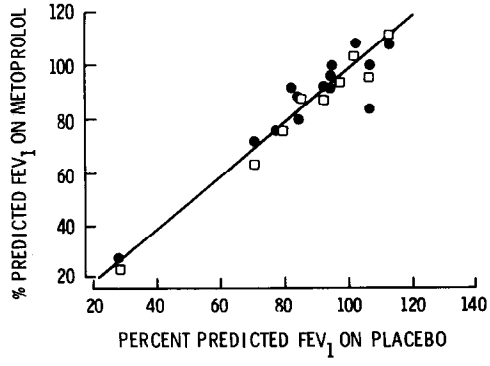

FIGURE 4. Percent change in forced expiratory volume in 1 second (FEV_1): placebo versus metoprolol after metaproterenol. **Closed circles,** metoprolol, 100 mg/day; **open squares,** metoprolol, 200 mg/day.

wide range of plasma propranolol levels (12 to 1,100 ng/ml). Interestingly, only one third of the patients responded at <160 mg/day of propranolol, while an additional 40% responded at propranolol doses of 200 to 640 mg/day. Thus, propranolol doses and plasma propranolol levels were frequently higher than comparable metoprolol doses in the present protocol. Propranolol has also been documented to suppress VT, especially if induced by exercise, a finding similar to the results of the present study.[3,17,18] Documentation of the ventricular antiarrhythmic effect of other beta-blockers, including tolamolol, alprenolol, and pindolol, lack studies utilizing long-term continuous ambulatory electrocardiographic recordings.[19–21] The duration of ambulatory electrocardiographic recording is crucial for appropriate evaluation of drug efficacy since recent studies emphasize a significant daily variability of ventricular arrhythmias.[22,23] In the present study, metoprolol at a dose of 100 mg/day suppressed only 34% of PVB, whereas 200 mg/day resulted in an overall 60% suppression of PVB. According to the data of Morganroth et al,[22] a 65% suppression of PVB is required to rule out variability as the cause of change in premature ventricular beat frequency in individual patients utilizing 3 days of placebo ambulatory electrocardiographic data and 3 days with the drug. By this criteria, high-dose metoprolol was "effective" in 50% of the 20 patients studied. The improved suppression of couplets (84%) and VT (94%), as well as abolition of exercise-induced VT, are all consistent with published observations of propranolol.[3,17]

This study also provides new information on plasma metoprolol levels achievable on routinely used dosage regimens as well as the degree of beta blockade demonstrated. High-dose metoprolol lowered the mean 24-hour heart rate from 78 to 62 beats/min while achieving a mean peak plasma metoprolol level of 72 ng/ml. This 20% decrease in the mean hourly heart rate during normal activity is similar to the 20 to 30% reduction in peak heart rate-blood pressure product documented by maximal exercise testing in this study. The wide range of peak plasma metoprolol levels (17 to 178 ng) obtained at steady-state doses of 200 mg daily are consistent with highly variable plasma propranolol levels[15,16] and emphasize the importance of clinical parameters to assess beta blockade. The lack of deterioration of resting left ventricular function or evidence for precipitation of clinical congestive heart failure even in patients with moderately depressed left ventricular function documents similar observations with other beta-blockers, even in the setting of acute myocardial infarction.[24–27,29] Experience from the National Beta-Blocker Heart Attack Trial demonstrated the ability of patients to tolerate significant doses of propranolol (160 to 320 mg/day) despite compensated congestive heart failure requiring digitalis and diuretics.[7] Similar observations were made during the Norweigan Metoprolol Trial, even with the use of intravenous metoprolol in the setting of acute myocardial infarction.[9]

Pulmonary function data were obtained because the use of metoprolol in many patients with obstructive lung disease may be desirable since the administration of nonselective beta-adrenergic blocking agents is precluded by bronchospasm. Several investigators have documented the relatively cardioselective effects of metoprolol compared with propranolol in patients with chronic bronchitis and asthma, although many reported studies used single metoprolol doses. Tivenius,[28] however, found little effect of metoprolol on ventilatory function in chronic airway obstruction after 4 doses of metoprolol; Formgren[29] documented a dose-related effect on FEV_1 in asthmatic patients taking metoprolol who were studied over a 17-day interval.

The current study illustrates the spectrum of functional ventilatory abnormalities that can be expected in patients with cardiac disease receiving metoprolol in doses to achieve a peak mean plasma metoprolol level of 72 ng/ml. We document the negative effects on FEV_1, FEF (25-75), and FVC, but emphasize that clinically significant deterioration in ventilatory function occurs only in a few select patients. The changes in FVC and FEV_1 are somewhat greater in our study than in reports by McGavin and Williams[30] and Sinclair.[31] This may be explained by our timing of pulmonary function tests, 2 hours after the test dose when drug levels are near peak. These changes in FEV_1 and FVC could not be explained due to alterations in left ventricular function with concomitant increase in lung water since there was no evidence of further echocardiographic or clinical left ventricular dysfunction with metoprolol.

Of the several patients who had measurable obstructive defects with decreasing FEV_1/FVC ratios and increasing airway resistance with metoprolol, only 1 had clinically significant wheezing. With the exception of that patient's response, the group data suggest that bronchodilator therapy obliterated these changes in FVC and FEV_1 induced by metoprolol. This further substantiates the findings of Thiringer and Svedmyr[32] and Johnson,[33] who reported that ventilatory changes induced by metoprolol were readily reversed by beta-adrenergic agonists but that those induced by propranolol were not. The availability of selective beta-2 adrenergic agonists such as albuterol may make concomitant therapy desirable, allowing the use of metoprolol when clinically indicated in these patients.

Our data further suggest that spirometry performed before and 2 hours after the first dose of metoprolol is useful to screen for pulmonary intolerance to beta-blocking agents. A decrease in FVC or FEV_1 of >20% from baseline would mandate special caution and constitute a relative contraindication to use of beta-blockers. A decrease of 10 to 20% from baseline could be corrected by the addition of a beta-2 selective agonist if the use of beta-blockers was indicated.

References

1. **Goldberg J, Frank C, Shapiro S.** Ventricular premature beats and mortality after myocardial infarction. N Engl J Med 1977;297:750–757.
2. **Vismara L, Amsterdam E, Mason D.** Relation of ventricular arrhythmias in the late hospital phase of acute myocardial infarction to sudden death after hospital discharge. Am J Med 1975;59:6–12.
3. **Nixon JV, Pennington W, Ritter W, Shapiro W.** Efficacy of propranolol in the control of exercise induced or augmented ventricular ectopic activity. Circulation 1978;57:115–122.
4. **Harrison TS, Dagher FJ, Paghen F, Beck L. Barttett J.** Rationale and indications for pre-operative adrenergic receptor blockade in pheochromo-

cytoma. Med Clin North Am 1969;53:1349–1358.
5. **Winkle R, Lopes M, Goodman D, Fitzgerald J, Schroeder J, Harrison D.** Arrhythmias in patients with mitral valve prolapse. Circulation 1975;52: 73–81.
6. **Turner J.** Propranolol in the treatment of digitalis-induced and digitalis-resistant tachycardias. Am J Cardiol 1966;18:450–457.
7. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction—mortality results. JAMA 1982;247:1707–1714.
8. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–807.
9. **Hjimarson A, Herlitz J, Malek I, Ryden L, Vedin A, Wadenstrom A, Wedel H, Elmfeldt D, Holmberg S, Nyberg G, Sedberg K, Waagstein F, Waldenstrom J, Wilhelmsen L.** Effect on mortality of metoprolol in acute myocardial infarction. Lancet 1981;2:823–827.
10. **Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL, Ribeiro LG, Miller RR.** A new simplified and accurate method for determining ejection fraction by two dimensional echocardiography. Circulation 1981;64:744–753.
11. **Morris JF, Kaski A, Johnson LC.** Spirometric standards for healthy non-smoking adults. Am Rev Respir Dis 1971;103:57–61.
12. **Goldman HI, Becklake MR.** Respiratory function tests: normal values at median altitudes and the prediction of normal results. Am Rev Tuber Pul Dis 1959;29:457–467.
13. **Boren HG, Kory RC, Snyder JC.** The Veterans' Administration-Army cooperative study of pulmonary function. Am J M 1966;41:96–114.
14. **Coltart DJ, Gibson DG, Shand DG.** Plasma propranolol levels associated with suppression of ventricular ectopic beats. Br Med J 1971;1:490–491.
15. **Coltart DJ, Shand DG.** Plasma propranolol levels in the quantitative assessment of β-adrenergic blockade in man. Br Med J 1970;3:731–734.
16. **Woosley RL, Kornhauser D, Smith R, Reele S, Higgins SB, Nies AS, Shand DG, Oates JA.** Suppression of chronic ventricular arrhythmias with propranolol. Circulation 1979;60:819–827.
17. **Winkle R, Gradman A, Fitzgerald J, Bell P.** Antiarrhythmic drug effect assessed from ventricular arrhythmias reduction in the ambulatory electrocardiogram and treadmill test: comparison of propranolol, procainamide and quinidine. Am J Cardiol 1978;42:473–480.
18. **Wennevold A, Sandoe E.** Propranolol (Inderal) in the long term prophylaxis of ventricular arrhythmias. Acta Med Scand 1968;183:87–89.
19. **Aronow W, Johnson L, Vangrove J, Nelson W, Khurseed M, Harding P.** Treatment of acute arrhythmias with orally administered tolamolol. Chest 1973;63:917–921.
20. **Anthony J, Jick H, Spodick D.** Control of persistent ventricular ectopic beats by alprenolol, a new beta adrenergic blocking agent. Am Heart J 1969; 77:598–602.
21. **Aronow W, Uyeyama R.** Treatment of arrhythmias with pindolol. Clin Pharm Ther 1972;13:15–22.
22. **Winkle RA.** Antiarrhythmic drug effect mimicked by spontaneous variability of ventricular ectopy. Circulation 1978;57:1116–1121.
23. **Morganroth J, Michelson E, Horowitz L, Josephson M, Pearlman A, Dunkman B.** Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 1978;58: 408–414.
24. **Lemberg L, Castellanos A, Arcebal A.** The use of propranolol in arrhythmias complicating acute myocardial infarction. Am Heart J 1970;80:479–487.
25. **Sandler G, Pisteros AC.** The use of oxeprenolol in cardiac arrhythmias associated with acute myocardial infarction. Br Med J 1971;1:254–257.
26. **Briant R, Norris R.** Alprenolol in acute myocardial infarction: double blind trial. N Z Med J 1970;71:135–138.
27. **Evemy K, Pentecost B.** Intravenous and oral practolol in the acute stages of myocardial infarction. Eur J Cardiol 1978;7:391–398.
28. **Tivenius L.** Effects of multiple doses of metoprolol and propranolol on ventilatory function in patients with chronic obstructive lung disease. Scand J Respir Dis 1976;57:190–196.
29. **Formgren H.** The effect of metoprolol and practolol on lung function and blood pressure in hypertensive asthmatics. Br J Clin Pharmacol 1976;3: 1007–1014.
30. **McGavin CR, Williams IP.** The effects of oral propranolol and metoprolol on lung function and exercise performance in chronic airway obstruction. Br J Dis Chest 1976;72:327–332.
31. **Sinclair DJM.** Comparison of effects of propranolol and metoprolol on airways obstruction in chronic bronchitis. Br Med J 1979;1:168.
32. **Thiringer G, Svedmyr N.** Interaction of orally administered metoprolol, practolol, and propranolol with isoprenaline in asthmatics. Eur J Clin Pharmacol 1976;10:163–170.
33. **Johnson G.** Use of a β-adrenoreceptor blockers in combination with β-stimulators in patients with obstructive lung disease. Drugs 1976;11: 171–177.