Metoprolol Minimizes Nighttime Blood Pressure Dip in Hypertensive Black Males

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Twelve hypertensive black males completed the study, which was conducted to evaluate the effect of metoprolol on 24-h ambulatory blood pressure (ABP). Study participants took 50 mg to 100 mg metoprolol twice daily for a minimum of 3 weeks. Metoprolol had no significant effect on blood pressure (147/90 ± 11/8 mm Hg *v* 151/88 ± 16/8 mm Hg, baseline *v* treated, respectively) in spite of causing significant reductions in heart rate (87 ± 9 beats/min *v* 69 ± 7 beats/min, $P < .001$). Only one subject had a ≥10 mm Hg decrease in 24-h diastolic blood pressure. The nighttime fall in blood pressure was minimized by metoprolol and clinically significant increases in daytime or nighttime blood pressure were noted in 58% of patients. Metoprolol therapy failed to lower blood pressure and eliminated the normal nighttime decline in blood pressure. Since the nighttime decline in blood pressure is thought to protect against target organ damage, it may be important to identify antihypertensive agents which preserve or enhance the nighttime blood pressure dip. Am J Hypertens 1995, 8:254–259

KEY WORDS: **Metoprolol, blacks, ambulatory blood pressure, diurnal.**

Ambulatory blood pressure monitoring (ABPM) is being used with increasing frequency in hypertension studies because it may be better correlated with target organ damage than clinic blood pressures.[1,2] ABPM is also being more commonly used to determine the antihypertensive effects of drugs. While there are some studies describing ambulatory blood pressure patterns in blacks, there are few studies which specifically describe the effects of antihypertensive agents on the 24-h ambulatory blood pressure (ABP) of blacks.[3,4] Such information may be important for several reasons. First, hypertension is a greater health problem in blacks. It is estimated that 40% of black American adults have hypertension, a percentage which is much higher than in white adults.[5] Hypertension also develops at an earlier age, is greater in severity, and is associated with a higher incidence of target organ damage in blacks than in whites.[5] Secondly, there is increasing literature that the 24-h pattern of ambulatory blood pressure differs between blacks and whites, such that blacks have a smaller decrement in nighttime blood pressure.[6–11] Lower daytime-nighttime blood pressure differences have been associated with greater target organ damage,[1,12,13] thus knowledge about the effect of antihypertensive agents in blacks, particularly during the nighttime, may be important. Finally, it is well recognized that blacks differ from whites in their clinic blood pressure response to many antihypertensive agents.[14,15] Because ABPM may better reflect the true antihypertensive effect of drugs, it is important to know the effects of antihypertensive agents on the 24-h ABP in blacks. Thus, the purpose of this study was to describe the effect of metoprolol on the 24-h ABP pattern in hypertensive blacks.

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METHODS

Study Population Fourteen black males with essential hypertension participated in the study, although only 12 were included in the data analysis because two had missing ABP data. Patients were eligible for inclusion in the study if they had newly diagnosed hypertension or had been untreated for at least 2 weeks prior to study initiation. A sitting diastolic blood pressure (DBP) ≥95 mm Hg on two separate visits at least 1 week apart was required for inclusion in the study. Blood pressure inclusion was based on clinic blood pressures determined by mercury sphygmomanometer, not 24-h ambulatory blood pressures. Exclusion criteria included: DBP >115 mm Hg, systolic blood pressure (SBP) ≥200 mm Hg, heart rate <55 beats/min, angina pectoris, insulin-dependent diabetes mellitus, bronchospastic lung disease, congestive heart failure, heart block, presence of a cardiac pacemaker, or recent (within 3 months) myocardial infarction or cerebrovascular accident. The study was conducted in the University of Tennessee Prevention Center and was approved by the University of Tennessee Institutional Review Board. Each subject provided informed, written consent prior to participating in the study.

Study Protocol Data from routine laboratory analyses, a complete blood count with differential, urinalysis, and 12-lead electrocardiogram were collected from each patient prior to initiation of the study.

Subjects underwent a 24-h period of ambulatory blood pressure monitoring (ABPM) once they met the blood pressure inclusion criteria. At the time of monitor placement, blood pressure determined by the ambulatory blood pressure monitor was checked against blood pressure determined by mercury sphygmomanometer. Subjects were sent home with the blood pressure monitor only if the two measurements were within 5 mm Hg of each other for both SBP and DBP. During the period in which ambulatory blood pressure was measured, subjects were instructed to conduct their normal daily activities. Ambulatory blood pressure and heart rate were determined and recorded using a portable, noninvasive, auscultatory recorder (Accutracker I, Suntech Medical Instruments, Inc., Raleigh, NC). Random measurements of blood pressure and heart rate were taken approximately four times per hour between 0600 and 2300 h and approximately twice per hour between 2300 and 0600 h. Following completion of the baseline 24-h ABPM, subjects were started on 50 mg metoprolol twice daily with target blood pressures of DBP <90 mm Hg and SBP <150 mm Hg. Following 2 weeks of therapy, subjects with clinic blood pressures less than 150/90 were continued on 50 mg metoprolol twice daily for a minimum of 1 additional week. Metoprolol dosage was increased to 100 mg twice daily in subjects who did not achieve the target blood pressure and they continued on that dosage for a minimum of 3 weeks. Following a minimum of 3 weeks on the final metoprolol dosage (50 mg or 100 mg twice daily) the subjects returned to the clinic for a second (treatment period) 24-h ABPM.

Data Analysis Editing criteria for exclusion of possibly erroneous ABP data included: SBP readings >260 or <70 mm Hg, DBP readings >150 or <40 mm Hg and pulse pressure readings of >150 or <20 mm Hg.[16] Artifactual readings (ie, due to arm movement during recording or poor sound quality) were noted by the recorder and were also considered for exclusion. ABPM data were not accepted if more than 25% of readings were excluded. Average blood pressure and heart rate were calculated for three time intervals: 1) 24 h, which included all acceptable data during a 24-h recording period, 2) daytime, which included acceptable readings taken from 0600 to 2300 h, and 3) nighttime, which included acceptable readings taken from 2300 to 0600 h.

Paired data were compared using paired, two-tailed Student's t test. It was noted that some patients had marked increases in blood pressure during metoprolol therapy. Clinically significant increases in blood pressure have previously been defined as an increase of ≥10 mm Hg in SBP or ≥5 mm Hg in DBP.[12] These criteria were used in determining the percentage of patients with clinically significant increases in blood pressure during metoprolol therapy. Comparisons of the frequency of significant blood pressure elevation were made by χ^2 tests. Data are presented as mean ± SD. Statistical significance was defined as $P < .05$. All statistical analyses were performed using Systat v.5.2 (Systat, Inc., Evanston, IL).

RESULTS

All 14 subjects completed the study; however, two of the subjects had greater than 6 h of missing ambulatory blood pressure data and therefore were not included in the data analysis. Ten of the remaining 12 subjects were taking 100 mg metoprolol twice daily at the end of the study, the other two subjects were taking 50 mg twice daily. The average age of the subjects was 43.7 years (range 29 to 55 years). Of the 12 subjects included in the data analysis, two were newly diagnosed hypertensives, eight were taking antihypertensive medications at the time of their first screening visit, and two were previously diagnosed hypertensives who were not taking any antihypertensive medications.

Based on ambulatory blood pressure data, metoprolol failed to produce an antihypertensive response in the group of 12 hypertensive black males included

in this study, independent of whether 24-h, daytime, or nighttime data were evaluated (Table 1). Average 24-h ambulatory blood pressures at baseline and during metoprolol therapy are shown for each subject in Figure 1. Only one subject had a ≥10 mm Hg drop in 24-h DBP. Mean hourly blood pressures at baseline and during metoprolol therapy are shown in Figure 2. Although clinic blood pressures were not the primary response measure in this study, they were recorded. Mean ± SD clinic blood pressures at baseline and during metoprolol therapy were 161/104 ± 15/8 mm Hg and 149/97 ± 21/9 mm/Hg, respectively. Based on clinic blood pressure data, three subjects (25%) had either a DBP <90 mm Hg or a ≥10 mm Hg decrease in DBP during metoprolol therapy. In spite of the lack of blood pressure response to metoprolol, there was an average decrease in 24-h heart rate of 21%, with all subjects exhibiting a decrease in heart rate during metoprolol therapy. Thus, the heart rate data suggest that the lack of blood pressure response to metoprolol cannot be explained by a lack of β-adrenergic receptor blockade.

Another finding was that metoprolol therapy diminished the diurnal variation in blood pressure. As can be seen in Table 1, nighttime blood pressure was significantly lower than daytime blood pressure during the baseline (drug-free) ABP studies. The percent decreases from day to night in systolic, diastolic, and mean blood pressure during the baseline phase were 8.5 ± 8.4%, 9.9 ± 9.1% and 9.3 ± 8.3%, respectively. Metoprolol therapy eliminated this nighttime fall in blood pressure such that daytime and nighttime blood pressures were essentially identical during the metoprolol therapy phase. The attenuation in the nighttime blood pressure dip, particularly for SBP, is also evident in Figure 2.

TABLE 1. AMBULATORY BLOOD PRESSURES AT BASELINE AND DURING METOPROLOL THERAPY

	Baseline	Metoprolol
Average 24-h data		
SBP (mm Hg)	147 ± 11	151 ± 16
DBP (mm Hg)	90 ± 8	88 ± 8
Heart rate (beats/min)	87 ± 9	69 ± 7*
Average daytime data		
SBP (mm Hg)	149 ± 10	152 ± 15
DBP (mm Hg)	92 ± 7	89 ± 8
Heart rate (beats/min)	89 ± 10	70 ± 7*
Average nighttime data		
SBP (mm Hg)	137 ± 18†	149 ± 25
DBP (mm Hg)	83 ± 11†	84 ± 10
Heart rate (beats/min)	81 ± 10†	66 ± 9*†

Mean ± SD.

*P < .001, *baseline* v *metoprolol.*

†P < .05, *daytime* v *nighttime during the same study phase.*

As can be seen in Figure 1, some patients had significant increases in blood pressure during metoprolol therapy. Based on the definition of clinically significant increases provided in the Methods section (increases of ≥10 mm Hg in SBP or ≥5 mm Hg in DBP), 8% of subjects had clinically significant increases in daytime SBP and 25% of subjects had clinically significant increases in daytime DBP. Likewise, 42% and 33% had clinically significant increases in nighttime SBP and DBP, respectively. Figure 2 shows that mean SBP was higher during metoprolol therapy at most timepoints between 1800 and 0800 h. The frequency with which SBP was increased was significantly greater at night than during the day ($P < .05$), while there was no difference in the frequency of DBP elevation between daytime and nighttime. A total of 58% of the study population met the criteria at least once for a clinically significant increase of SBP or DBP during either the daytime or nighttime.

Baseline characteristics in patients with clinically significant increases in blood pressure were not different from those without significant increases in blood pressure. Specifically, there were no differences between groups in mean baseline 24-h, daytime, or nighttime blood pressure, heart rate, baseline laboratory values, the percent taking blood pressure medication at the time of screening for the study, or the percentage of smokers.

DISCUSSION

Metoprolol therapy failed to decrease blood pressure in this group of 12 hypertensive black men. Heart rate declined significantly during metoprolol therapy in all subjects, thus the lack of overall blood pressure lowering effect does not appear to be related to a lack of β-adrenergic receptor blockade.

Metoprolol also eliminated the nighttime fall in blood pressure, a finding which may be important for several reasons. Several studies have documented that a low daytime-to-nighttime difference in blood pressure is associated with a higher degree of target organ damage.[1,10,11] Thus, the nighttime dip in blood pressure may help protect against the complications of hypertension. With regard to blacks, data from a number of studies suggest that they have a smaller nighttime fall in blood pressure than whites,[6–11] although this is not a universal finding.[17,18] In one study, black hypertensives had 8% and 9% decreases in SBP and DBP, respectively, from daytime to nighttime, which was significantly different from the 14% decreases in SBP and DBP observed in white hypertensives.[9] This ethnic difference in the diurnal blood pressure pattern has been suggested as an explanation for the higher incidence of target organ damage in black than in white hypertensives.[6,9] In our study, we showed 8.5% and 9.9% decreases in baseline SBP

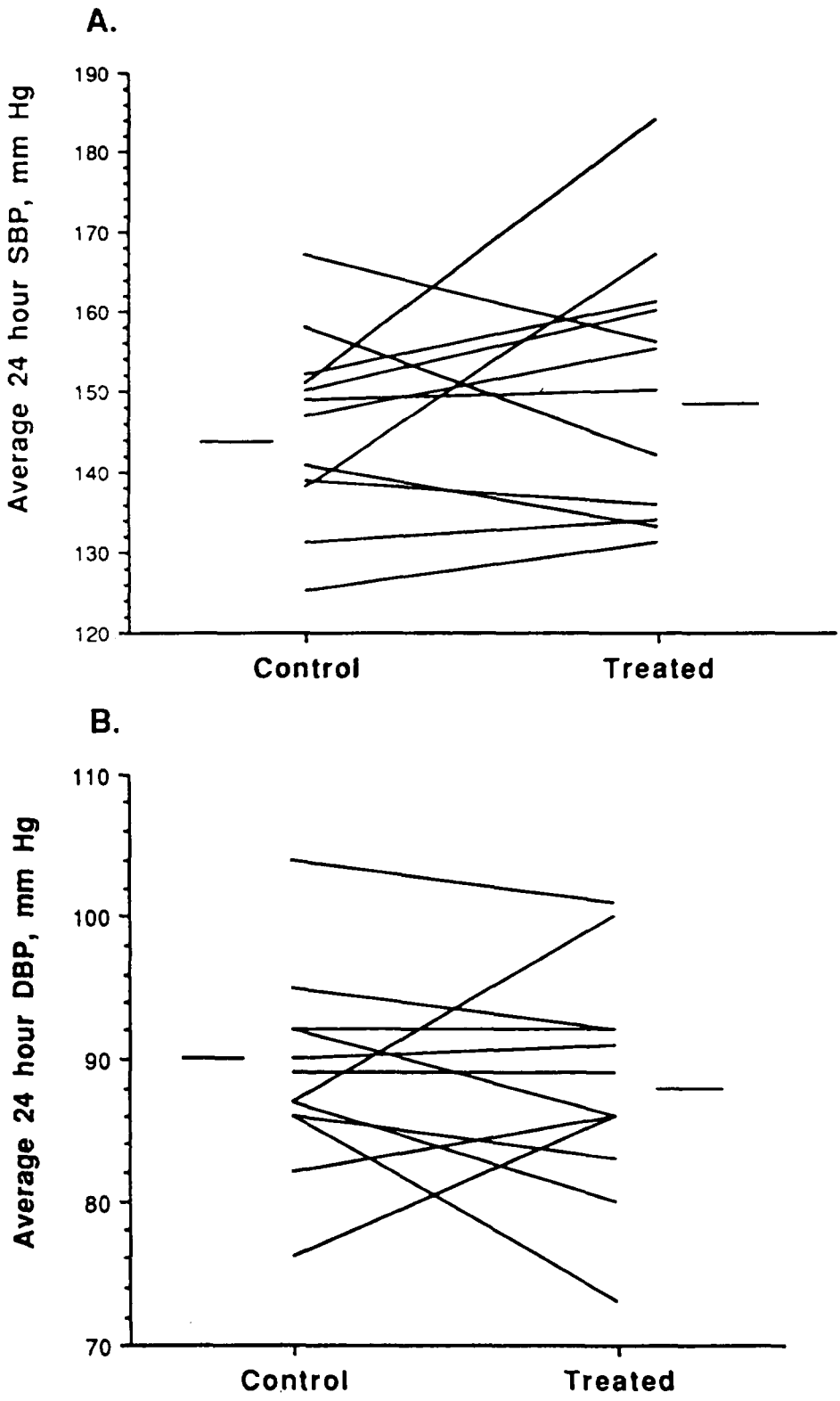

FIGURE 1. *Average 24-h blood pressures at control and during metoprolol therapy in each subject. Solid bars represent mean values. A) Average 24-h SBP; B) average 24-h DBP.*

and DBP, respectively, from daytime to nighttime, similar to the findings of Murphy et al.[9] However, this nighttime fall in blood pressure was eliminated by metoprolol. If the nighttime decline in blood pressure helps to protect against target organ damage, then metoprolol's lack of antihypertensive effect, coupled with its elimination of the nighttime blood pressure dip, could be viewed as an overall detrimental effect of the drug in this group of hypertensive black men.

It is not clear from the limited literature whether the detrimental effect of metoprolol on diurnal blood

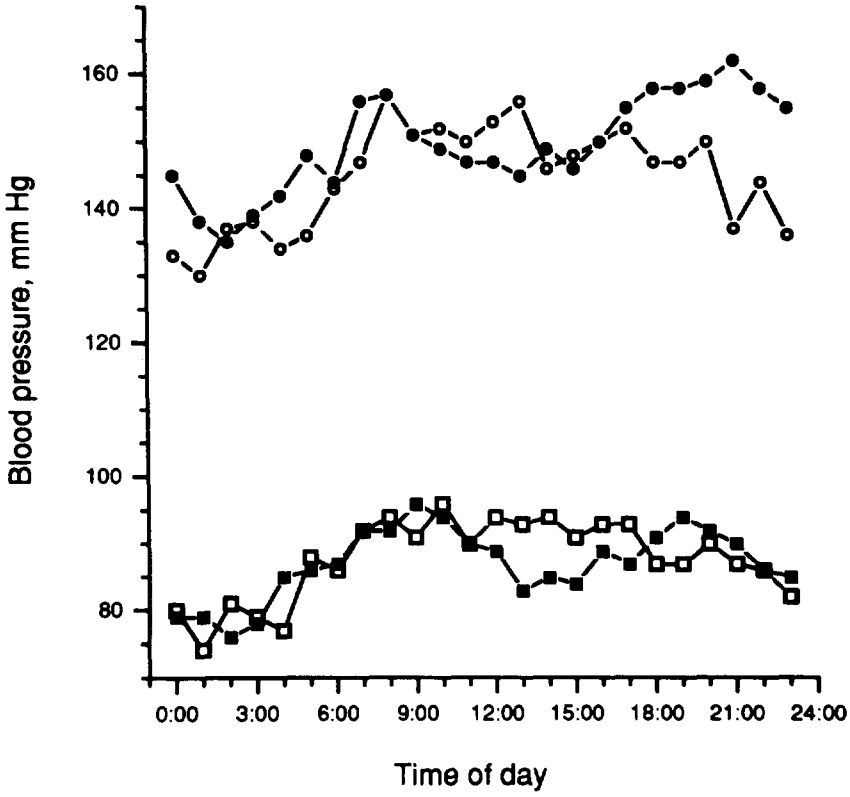

FIGURE 2. *Mean hourly systolic and diastolic blood pressures at baseline and during metoprolol therapy. Key: ○, SBP at baseline; □, DBP at baseline; ●, SBP during metoprolol therapy; ■, DBP during metoprolol therapy.*

pressure variation observed in this small study represents β-blocker class effect, a metoprolol-specific effect, or a racial difference in drug response. An ABP study with atenolol, propranolol, metoprolol, and pindolol suggests that atenolol and propranolol have positive nighttime blood pressure effects, while metoprolol appeared to eliminate the nighttime dip and pindolol's effects were intermediate.[19] In two other studies with atenolol, one suggests good antihypertensive effect at nighttime,[20] while the other suggests that atenolol may somewhat attenuate the nighttime blood pressure decline.[21] The only study of which we are aware that describes the effects of a β-blocker on ABP in blacks described 24-h responses and not daytime and nighttime responses specifically.[3] Further studies will be necessary to clarify the effects of β-blockers on nighttime blood pressure in blacks and whites.

Fifty-eight percent of subjects in this study had a clinically significant increase in their average daytime or nighttime blood pressure during metoprolol therapy. Although this finding is somewhat surprising, our data are not inconsistent with the literature. In a study by Cruickshank et al,[22] five of 25 (20%) black hypertensive patients had clinically significant increases in daytime SBP during metoprolol therapy. In a VA Cooperative Study, 6.4% of black hypertensives had clinically significant increases in daytime SBP.[12] These data compare similarly with the 8% of our patients with clinically significant increases in daytime SBP. An important point from our study is that most of the blood pressure elevation with metoprolol occurred between 1800 and 0800 h (Figure 2), the hours when a patient is least likely to have blood pressure monitored by a health care professional. Thus, studies which measured blood pressures in the clinic (and therefore during the day) may have missed the effect of blood pressure elevation by metoprolol or other β-blockers.

A major limitation of this study is the small sample size. Questions that could be clarified in larger studies include 1) whether our findings are reproducible in a larger population of blacks, 2) whether metoprolol would have a similar negative impact on nighttime blood pressure in whites, and 3) whether the effect observed in this study is unique to metoprolol or occurs with other β-blockers. A possible explanation for the findings in this study is that many of the subjects were relatively dependent on β_2-receptor–mediated vasodilation for maintenance of blood pressure. Therefore, blockade of β_2 receptors may have tipped the balance between the α- and β-receptor systems in the peripheral vasculature, resulting in α-receptor–mediated vasoconstriction and an increase in blood pressure. The assumption in this hypothesis is that β_2 receptors are being blocked by the relatively β_1-selective blocker, metoprolol. However, the β_2-receptor blocking effects of normal doses of metopro-

lol have been well described,[20] thus this assumption seems reasonable.

Another possible explanation for these findings is that these hypertensives had a lower cardiac output during metoprolol therapy which resulted in adverse sympathetic nervous system activation or increased renin feedback.[24] We did not measure cardiac output or peripheral plasma renin activity in this study, thus complex hemodynamic interactions cannot be assessed.

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