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Case Reports

24-Hour Blood Pressure Recording in Patients with Orthostatic Hypotension

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Summary: Continuous intra-arterial blood pressure measurement and electrocardiograms were obtained in two ambulatory patients with orthostatic hypotension due to autonomic dysfunction. Systolic and diastolic arterial pressure presented marked variations which took place mainly during the day and were related to several physical activities; however, marked falls in blood pressure were also observed during sleep and at the monent of arousal. A peak incidence of hypotensive events was found in the afternoon, mainly in the hours following the afternoon meal. Recording was repeated after 3 weeks of treatment with propranolol, 40 mg t.i.d. In patient 1, beta blockade drastically reduced the number and severity of hypotensive episodes, while propranolol failed to control blood pressure in patient 2, who experienced a higher number of hypotensive events during treatment. Findings of this study may be relevant to the management of patients with orthostatic hypotension and should contribute to a more accurate characterization of blood pressure profile in autonomic dysfunction.

Key words: postural hypotension, autonomic dysfunction, intra-arterial blood pressure recording, propranolol

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Introduction

Severe orthostatic hypotension is a relatively rare condition in which a marked fall in blood pressure occurs when the patient assumes the upright position. Many previously described cases were considered a consequence of a failure in reflex adrenergic response, mostly due to a lesion in the efferent sympathetic pathway (Bannister, 1979; Ibrahim, 1975). Ziegler *et al.* (1977) related the deficiency of sympathetic nervous reflex activity to decreased norepinephrine release on standing. More recently, it has been suggested that postural hypotension may be the consequence of an imbalance in alpha- and beta-adrenoceptor activity in the peripheral nervous system (Brevetti *et al.*, 1979). Furthermore, Huy and Connolly (1981) demonstrated an increased number of beta adrenoceptors in orthostatic hypotension due to autonomic dysfunction. This impairment of neurohormonal mechanisms, which in normal subjects allows the maintenance of the pressure homeostasis, conceivably may affect the regulation of blood pressure during other functions involving sympathetic activity. Accordingly, the relationship between blood pressure and sleep, waking, and physical activities has been investigated by 24-h continuous blood pressure recording in two patients with orthostatic hypotension. An additional goal of this study was to verify the efficacy of treatment with propranolol, previously described to be beneficial in orthostatic hypotension (Brevetti *et al.*, 1981; Chiariello *et al.*, 1983).

Subjects and Methods

Once informed consent was obtained from the patients, intra-arterial pressure was recorded continuously for 24 h on a miniaturized tape recorder (Oxford Instruments

Ltd.) from a cannula inserted percutaneously into the left brachial artery. A simultaneous electrocardiogram was recorded on a second channel from chest electrodes. Patients were allowed to go about their normal daily routine in the hospital and significant events were recorded by marking the tape and also in a diary kept by the patients.

Two males with autonomic dysfunction ages 63 and 66, respectively, were hospitalized because of recurrent attacks of syncope. Both complained of increased urinary frequency, constipation, lack of sweating, and slowness of movements. Neither presented disorders known to be associated with secondary orthostatic hypotension. The standard 12-lead electrocardiogram revealed anterior myocardial ischemia in patient 1, and anterolateral myocardial ischemia with frequent atrial premature beats in patient 2. In both patients echocardiograms did not show cardiac abnormalities. Testing of autonomic function demonstrated pronounced postural hypotension, loss of systolic overshoot during Valsalva manoeuver, and a normal blood pressure decrease during hyperventilation in both patients. Cold pressor testing induced a paradoxical fall in blood pressure in patient 1 and a normal rise in patient 2. Normal resting levels of plasma norepinephrine, which did not increase on standing were found in patient 2. On the contrary, patient 1 showed low supine plasma levels of norepinephrine (153 μg/ml), which did not increase on standing.

After the first 24-h recording of arterial pressure, propranolol 40 mg t.i.d. was started in both patients and a second blood pressure ambulatory monitoring was performed 3 weeks later. The tape recordings were initially replayed and written out in full using a pen recorder. Values of blood pressure were computed using a hybrid computer and data were pooled. Mean values for each hour of a 24-h cycle were then calculated. The number of hypotensive episodes occurring before and during treatment were also evaluated.

Finally, the mean systolic pressure for 24 h was calculated, and the integrated areas delimited by systolic pressure below this value were measured. This allowed a more accurate evaluation of the hypotensive episodes, taking into account the number, duration, and severity of the events (Fig. 1).

Data obtained before and during treatment were expressed as mean $\pm$ standard error and were compared using Student's *t*-test for paired samples.

Results

In control subjects (example in Fig. 2), blood pressure falls during sleep, increases in the early hours of the morning, before waking, and presents the major rise at the moment of arousal. Usually no substantial changes can be observed during the day. On the contrary, in patients with orthostatic hypotension (patient 2 in Fig 2), continuous 24-h arterial pressure monitoring shows marked variations in both systolic and diastolic pressure. The changes can be observed mainly while the patients are awake and are related to several physical activities; however, during sleep, abrupt and marked falls in blood pressure can also be recorded. Blood pressure rises progressively in the early hours of the morning before waking and abruptly falls at the moment of arousal (Fig. 2). Contrary to what is observed in normal subjects, progressive decreases in systolic and diastolic blood pressures without changes in heart rate are observed following meals.

The individual plots of mean arterial pressure obtained before and during propranolol therapy in our two patients are depicted in Figures 3 and 4. Patient 1 showed a marked variability of arterial pressure both during the day and night; propranolol induced a constant increase in arterial pressure, mainly during the night and reduced the variability. Actually the mean daytime value of mean arterial pressure was 86.0 ± 16 mmHg before propranolol and 98.0 ± 11 mmHg ($p < 0.02$) during treatment. In the night, i.e., from the moment when the patient went to bed to the moment of arousal as recorded in the diary, mean arterial pressure was 89.5 ± 10 mmHg under control conditions and 113.7 ± 4 mmHg ($p < 0.001$) during propranolol.

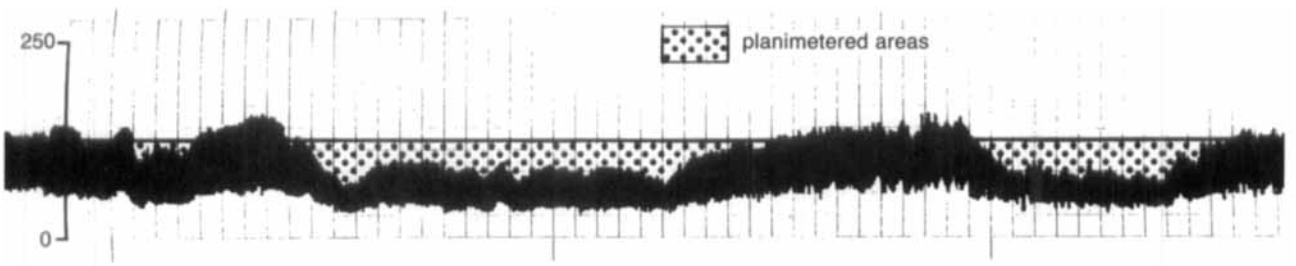

FIG. 1 Example of the method utilized in evaluating the hypotensive events. Falls in systolic blood pressure below the 24-h mean systolic pressure (continuous line) were considered and the dotted areas between this value and the peaks of systolic blood pressure were calculated by means of a computer. This method allows an accurate quantification of the hypotensive events, taking into account the number, the duration, and the severity of the events.

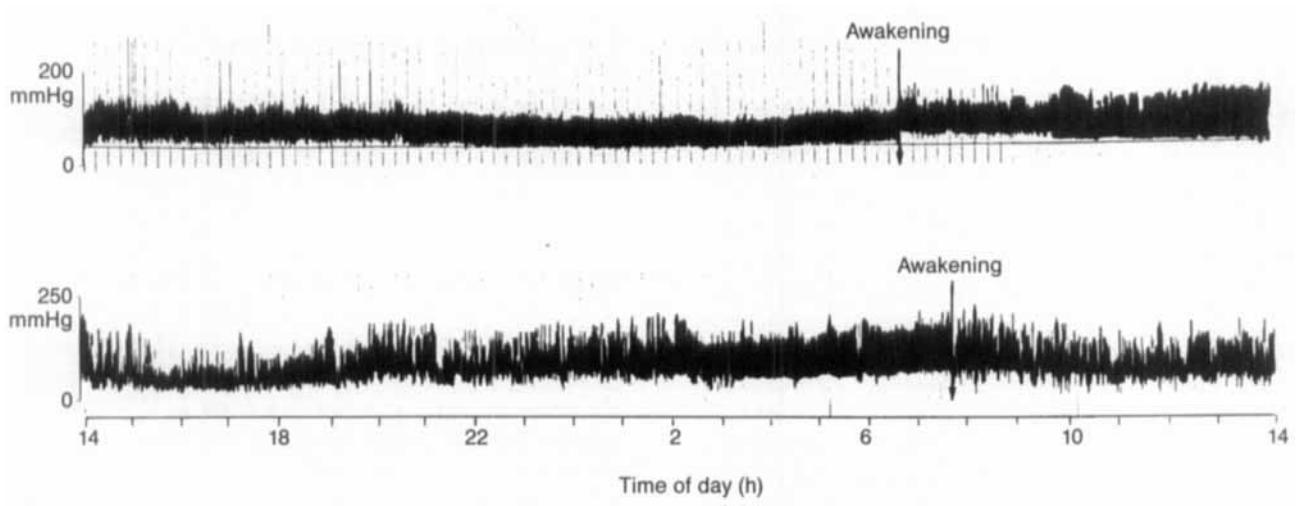

FIG. 2 24-h blood pressure recording in a normal subject (upper graph) and in a patient with orthostatic hypotension (patient 2, lower graph). Note the frequent marked variations in systolic and diastolic pressure and the sharp fall in blood pressure at the moment of arousal occurring in this patient.

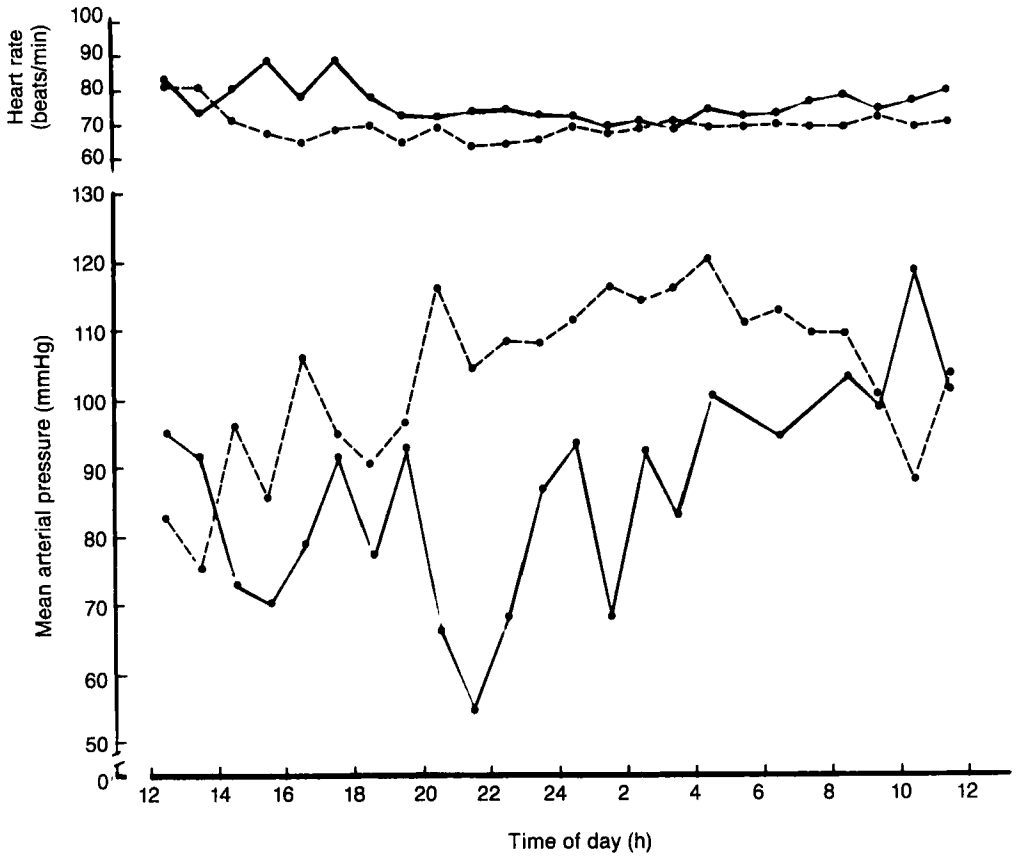

FIG. 3 Trends in heart rate (upper panel) and mean arterial pressure (lower panel) obtained before (•——•) and during propranolol (•---•), in patient 1.

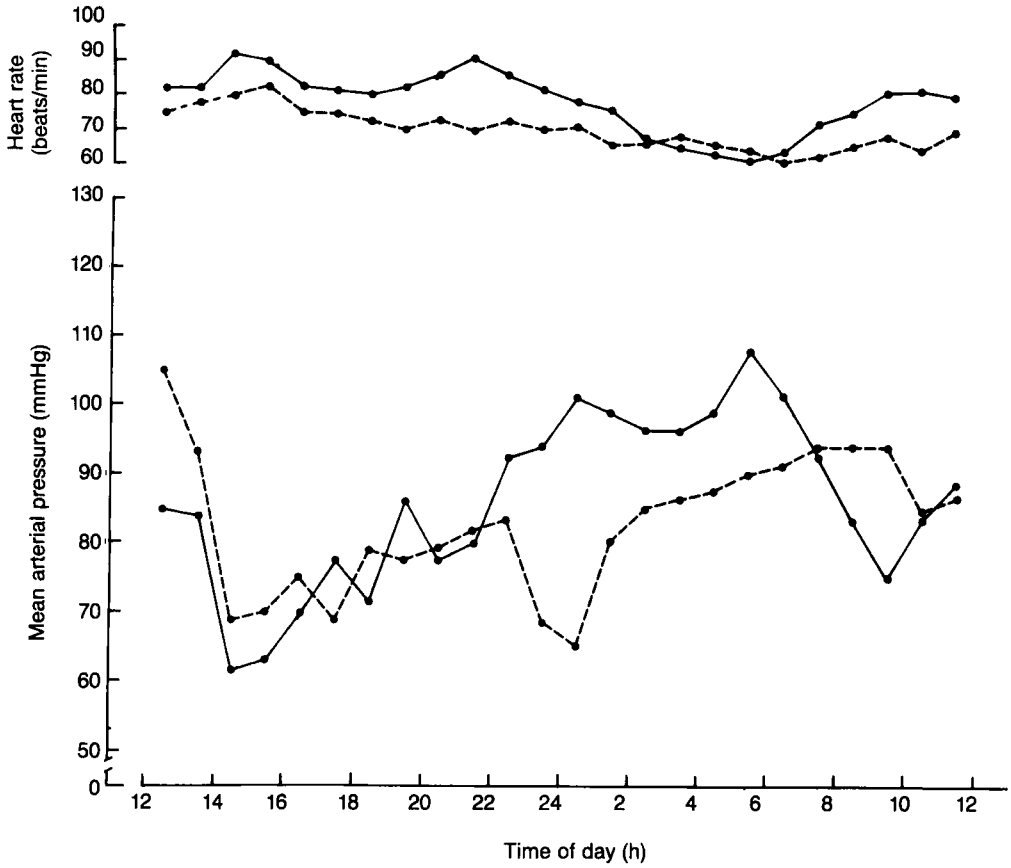

FIG. 4 Trends in heart rate (upper panel) and mean arterial pressure (lower panel) obtained before (•——•) and during propranolol (•---•), in patient 2.

In patient 2 the circadian trend was the reverse of that observed in normals: the lower pressures occurring during the day the higher ones in the night. This pattern was affected by propranolol, which did not modify arterial pressure in the day and drastically reduced it during the night. Actually, during the day mean arterial pressure was 79.5 ± 9 and 82.9 ± 10 mmHg before and during propranolol, respectively, while during the night it was 99.5 ± 12 mmHg before treatment and 83.2 ± 4 mmHg ($p < 0.01$) during propranolol.

Dramatic falls in blood pressure, from 160/80 to 60/20 mmHg and from 150/80 to 75/50 mmHg in patients 1 and 2, respectively, were recorded whenever they assumed the erect position. Therefore, on standing, systolic arterial pressure decreased by 62.5% and diastolic by 75% in patient 1; in the second patient, systolic arterial pressure decreased by 50% and diastolic pressure by 37.5%. These hypotensive events were not accompanied by a corresponding increase in heart rate. Propranolol blunted the fall in blood pressure in patient 1 evidenced by supine pressure of 175/100 mmHg decreasing to 110/70 mmHg in upright position. This represents a fall of 37.1% in systolic and 30% in diastolic arterial pressure. On the contrary, in patient 2, beta blockade failed to satisfactorily control blood pressure on standing. On propranolol, arterial pressure decreased from 150/80 to 70/30 mmHg, a 53.3% fall in systolic and 62.5% fall in diastolic blood pressure. In both patients, failure to maintain a normal blood pressure was observed not only in response to changes in posture, but also during other activities. Before treatment, a syncopal episode occurred in patient 1 during defecation. Similarly, severe hypotension was recorded during digestion and during the stress test that patient 2 performed in the supine position for removing the elastic stockings which he used as therapeutic support. The number of hypotensive episodes (abrupt fall in systolic pressure >30 mmHg occurring within a period of 2 minutes or less) is reported in Table I. Results show that these episodes were more frequent during the day and confirm that they were present also during the night. Moreover, the different therapeutic effects achieved by propranolol in the two patients is also clearly demonstrated. The total number of hypotensive episodes actually were reduced by propranolol from 68 to 37 in patient 1, while they increased from the control value of 61 to 99 during treatment in patient 2. Table II reports the number of hypotensive events with systolic arterial pressure ≤ 80 mmHg. Results confirm the different therapeutic effects

TABLE I Number of hypotensive episodes (falls in systolic arterial pressure >30 mmHg occurring within a period of 2 minutes or less)

	Number of episodes		Number of episodes/h	
Time interval (h)	Control	Propranolol	Control	Propranolol
Patient 1				
7-12	18	11	3.0	1.8
13-22	41	25	4.1	2.5
23-6	9	1	1.1	0.1
Total	68	37	2.8	1.5
Patient 2				
7-12	23	41	3.8	6.8
13-22	25	40	2.5	4.0
23-6	13	18	1.6	2.2
Total	61	99	2.5	4.1

TABLE II Number of hypotensive episodes with systolic arterial pressure ≤80 mmHg

	Number of episodes		Number of episodes/h	
Time interval (h)	Control	Propranolol	Control	Propranolol
Patient 1				
7-12	5	3	0.9	0.5
13-22	16	8	1.6	0.8
23-6	0	0	0	0
Total	21	11	0.8	0.4
Patient 2				
7-12	5	8	0.9	1.3
13-22	13	29	1.3	2.9
23-6	2	3	0.2	0.3
Total	20	40	0.8	1.6

of propranolol in the two patients and suggest that there is a higher incidence of severe hypotensive episodes in the afternoon.

Before treatment, 24-h mean systolic blood pressure was 122 ± 19 mmHg in patient 1 and 118 ± 14 mmHg in patient 2. The 24-h mean area comprised between these values and the systolic pressures below it, was 52.7 ± 9.5 cm^2 in patient 1, and 35.5 ± 6.9 cm^2 in patient 2. Both values were significantly higher (<0.005) than that measured in a control subject (14.1 ± 2.2 cm^2). During propranolol, 24-h mean systolic arterial pressure was 142 ± 14 and 119 ± 19 mmHg in patient 1 and 2, respectively. As compared to pretreatment values beta blockade significantly reduced the area to an extent as low as 39.5 ± 7.7 cm^2 ($p<0.05$) in patient 1 and did not modify it in patient 2, in whom it was 36.9 ± 4.3 cm^2. Results concerning these data are represented in Figure 5.

Discussion

In patients with autonomic failure, hemodynamic studies demonstrated paradoxical responses of arterial pressure not only to the assumption of erect position, but also to several induced stresses, such as exposure to cold, pain, mental arithmetic test, etc. (Barnett *et al.*, 1955; Ibrahim, 1975). These observations have been made in patients who have been restricted to bed for a period limited to the time of the study and, thus, have little relevance to blood pressure changes in patients exposed to normal environmental stress. Recently, Mann *et al.* (1983) monitored intra-arterial pressure in 6 ambulatory patients with autonomic dysfunction and found a consistent circadian trend in blood pressure, with the highest values in the night and the lowest in the morning. Since this pattern was not modified by confinement of the patients to bed, the authors ex-

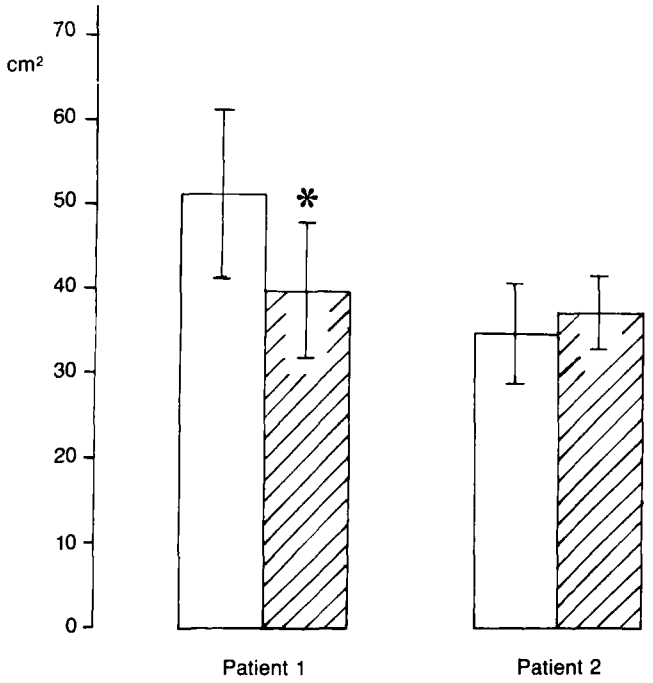

FIG. 5 Different effects of propranolol on the hypotensive events in the two patients. Columns indicate the 24-h mean values of the hypotensive areas below the mean systolic blood pressure, before (□) and during (▨) propranolol. *=$p<0.05$.

cluded that posture was the sole determinant of blood pressure variations in subjects with orthostatic hypotension.

The two patients reported in this study showed a different circadian trend in blood pressure. Patient 1 manifested a high variability of arterial pressure during the day as well as during the night; in contrast, patient 2 was similar to those described by Mann *et al.* (1983) showing the lowest arterial pressure during the day and the highest in the night. In both patients, however, the lowest levels of arterial pressure were always related to several physical activities such as awakening, digestion, etc. which induced severe hypotension independently from posture. The reduction of blood pressure on standing was recorded on many occasions during the study and a marked variability in postural hypotension was observed. Abrupt and marked falls in arterial pressure were also recorded in the night, during sleep. Since electroencephalograms were not obtained, it is not possible to relate these variations in pressure to sleep depth or to periods of rapid eye movement sleep. However, Richardson *et al.* (1968) by correlating the electroencephalogram with blood pressure noted that, in normals waking, even for brief periods, always resulted in elevation of blood pressure, which coincided with recurrence of alpha rhythm. Moreover, Floras *et al.* (1978) demonstrated a sharp increase in blood pressure on arousal similar to that obseved in our control subjects and suggested that it was due to sympathetic drive. These observations suggest that the hypotensive events observed in our patients during the night and at the moment of arousal may be considered as a paradoxical response of blood pressure to the activation of the sympathetic nervous system, therefore, representing an additional aspect of the autonomic dysfunction. A marked decrease in arterial pressure, which was not affected by propranolol, was observed in both patients during digestion. Similar results have been previously reported by Robertson *et al.* (1981) in autonomic dysfunction states and were referred, in part, to the depressor effect of arachidonic acid metabolites. Probably as a consequence of the depressor action of digestion, our patients, mainly those with a systolic blood pressure ≤ 80 mmHg, showed a higher incidence of orthostatic events in the afternoon.

In patient 1, propranolol blunted the fall in arterial pressure induced before treatment by orthostasis and other activities involving the sympathetic nervous system, and drastically reduced the number and severity of hypotensive episodes. On the contrary, beta blockade did not prevent orthostatic hypotension in patient 2, who experienced a higher number of hypotensive events during treatment. Different therapeutic effects of propranolol in patients with autonomic failure and orthostatic hypotension were previously referred to a different pathophysiologic mechanism (Chiariello *et al.*, 1983). Beta blockade is beneficial in those patients in whom orthostatic hypotension is accom-

panied by failure of peripheral vasoconstriction, while it is ineffective when the orthostatic fall in blood pressure is dependent exclusively on a decrease in cardiac output. Although in these patients cardiac output was not measured, it can be suggested that the different effects of propranolol in our 2 patients is related to the different type of mechanism underlying orthostatic hypotension. In any case, results of this study confirm a previous observation demonstrating the lack of therapeutic effect of propranolol in patients who, although suffering from orthostatic hypotension, exhibit a normal response to cold pressor testing and show a preserved vasoconstriction on standing (Chiariello *et al.*, 1983). Indeed, patient 2, who did not benefit from the treatment showed an increase in blood pressure during the cold pressor test.

An interesting finding of this study is that the different effects of beta blockade on arterial pressure were observed during the day (i.e., when the patients were engaged in physical activities), and also while sleeping. Actually, propranolol increased nocturnal arterial pressure in patient 1 and reduced it in patient 2 as compared to pretreatment values. This demonstrates that propranolol influences the different pathophysiologic mechanisms implicated in autonomic insufficiency independently from the posture or other activities.

The results of the ambulatory blood pressure monitoring in these patients may supply some guidelines for the management of patients with orthostatic hypotension. The clinical relevance of postprandial hypotension is attested to by the frequency with which patients themselves related reduced orthostatic tolerance to the postprandial period, as well as by the elevated number of hypotensive episodes recorded in the afternoon. Affected individuals should be warned against physical activity after meals. Furthermore, the potential harm induced by nocturnal hypotension should be prevented by appropriate intervention. Finally, since in some patients with orthostatic hypertension, propranolol treatment may be ineffective or even deleterious, extreme caution is necessary in the selection of patients receiving this drug.

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