Journal of Cardiology 1995; 25: 95–99

Reassessment of Circadian Profile of Blood Pressure and Heart Rate in Diabetic Patients With Autonomic Neuropathy

Samuel ZONERAICH
Ajay LODHA
Joseph TIBALDI
Ruth Bernstein HYMAN*
Joseph L MOLLURA

Abstract

Previous studies have shown that the normal circadian blood pressure fall is absent in patients with diabetic autonomic neuropathy, while the reported rise in blood pressure during the night in the same patients is controversial. This study analyzed the circadian profile in 19 diabetic patients with established autonomic neuropathy.

Twenty-four hour ambulatory systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate were recorded every 20 minutes during the day and every 60 minutes at night in 29 patients, 19 with diabetic autonomic neuropathy and 10 nondiabetic hypertensive patients as controls. Twelve diabetic patients with autonomic neuropathy with unknown hypertension were found to have hypertension based on 24 hour ambulatory blood pressure monitoring. Repeated measured analysis of variance (ANOVA) and trend analysis indicated that the linear systolic blood pressure increased from night to morning to afternoon while mean arterial pressure and diastolic blood pressure increased from night to morning but decreased from morning to afternoon. In practice, the early morning rise in systolic blood pressure in diabetic neuropathy is not different from that in normal or hypertensive patients and requires appropriate treatment. The absence of the nocturnal rise in the blood pressure revealed a subgroup of patients with diabetic neuropathy which demonstrated no fatal cardiovascular or renal events over 18 to 24 months of follow-up.

Key Words

autonomic nervous system (diabetic autonomic neuropathy), hypertension, ambulatory blood pressure

Twenty-four hour blood pressure monitoring in healthy subjects demonstrates a circadian rhythm, the lowest values occurring during sleep and the highest values during daytime[1,2]. Continuous intra-arterial blood pressure and electrocardiogram recordings obtained in 20 hypertensive patients revealed that the blood pressure was lowest at 3:00 a.m., began to rise during the early hours of the morning, reached the highest value mid-morning, and then fell during the remainder of the day[3].

An altered circadian profile of blood pressure in diabetic and non-diabetic patients with autonomic neuropathy has been reported[4,5]. The nocturnal fall of the blood pressure was absent or reversed. However, other workers have questioned the existence of a rise of the blood pressure during the night in diabetic patients with cardiac autonomic neuropathy[6]. The present report analyzed the circadian rhythms in subgroups of patients with cardiac autonomic neuropathy and hypertension and proposes possible

Division of Research, Cardiac Education and Hypertensive Center, Albert Einstein College of Medicine, Flushing Hospital & Medical Center Affiliate of the Flushing NY, and *Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Flushing, NY
Address for reprints: Samuel ZONERAICH, MD, FACC, Division of Research, Cardiac Education and Hypertensive Center, Flushing Hospital & Medical Center, 45th Avenue at Parsons Boulevard, Flushing, NY 11355, U.S.A.
Received for publication August 17, 1994; accepted October 18, 1994

practical therapeutic applications.

SUBJECTS

This study included 19 diabetic patients with autonomic neuropathy. Four patients had peripheral neuropathy. Six patients had retinopathy and two had associated gastropathy. Seven patients were receiving medication for hypertension. The other 12 patients were diagnosed as hypertensive by 24 hr ambulatory blood pressure monitoring. Blood pressures over 140/190 mmHg in more than 40% of recordings during 24 hrs were considered to indicate hypertension. The duration of diabetes was varied from 6 to 35 years (mean 16.5 yrs). Fifteen patients were receiving insulin, and 4 oral hypoglycemic agents.

The total glycosylated hemoglobin values (ISO Lab. affinity column) ranged from 7.1 to 18 (mean 11.8) in 11 patients. Albuminuria (total protein > 300 mg/24 hrs) was noted in 12 patients. All but two patients had abnormal blood urea nitrogen levels. The creatinine level was within the normal range in all patients but one.

Ten nondiabetic hypertensive patients, matched for age and sex, were included in the control group.

Definition of subgroups

Control group : Ten nondiabetic hypertensive patients with a history of hypertension and receiving medication; 7 males (mean age 65.2 yrs), 3 females (mean age 47 yrs), 24 hr mean arterial pressure 105.40±11.82 mmHg (mean±SD).

Diabetic patients with cardiac autonomic neuropathy and known hypertension : Seven patients; 3 males (mean age 59.6 yrs), 4 females (mean age 59.5 yrs), 24 hr mean arterial pressure of 103.50±7.57 mmHg.

Diabetic patients with cardiac autonomic neuropathy and hypertension discovered by 24 hr ambulatory blood pressure monitoring : Twelve patients, 7 males (mean age 62.5 yrs) and 5 females (mean age 58.5 yrs), 24 hr mean arterial pressure of 104.50±9.71 mmHg.

METHODS

Autonomic testing

The diabetic patients with autonomic neuropathy underwent cardiovascular reflex testing.

1. The Valsalva test (reported in 1704 by Antonio Maria Valsalva) : Heart rate variability ratio of 1.2 in different phases of respiration was considered positive[7].
2. Circadian variations defined as a difference of 10/5 mmHg or more between mean daytime blood pressure and mean nighttime blood pressure.
3. Orthostatic hypotension with a standing decrease of more than 20 mmHg in systole and of more than 10 mmHg in diastole, without an appropriate increase in pulse rate.

At least two positive results were considered to indicate cardiac autonomic neuropathy.

Twenty-four hour recording

Twenty-four hr ambulatory blood pressure, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate were recorded every 20 min during the day and every 60 min during the night in all diabetic patients and control patients (Spacelab 90229). Circadian variation was defined as a difference of 10/5 mmHg or more between mean daytime blood pressure and mean nighttime blood pressure[8].

Statistical analysis

Differences in the patterns of blood pressures over night, morning, and afternoon between hypertensive patients with and without diabetes were tested using repeated measures analysis of variance (ANOVA) tests and trend analysis, with a significant interaction hypothesized for each analysis. Two sets of analyses were done, one using the three groups separately, and one combining the two groups of hypertensives with diabetes and autonomic neuropathy for comparison with the hypertension only group. Each set of analyses included four repeated measures ANOVA tests for the four dependent variables : systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate.

RESULTS

Linear and quadratic trends were significant for systolic blood pressure, diastolic blood pressure and mean arterial pressure (MAP). The effect for time was statistically significant as follows :

3 groups MAP $p=0.000$	2 groups MAP $p=0.000$
3 groups systolic $p=0.000$	2 groups systolic $p=0.000$
3 groups diastolic $p=0.000$	2 groups diastolic $p=0.000$

For all three variables, both the linear and quadratic trends were statistically significant at $p<$

0.05, indicating a linear increase of the blood pressure from night to morning and a bend in the curve from morning to afternoon. Systolic blood pressure increased from night to morning to afternoon (**Fig. 1**). Mean arterial pressure (**Fig. 2**) and diastolic blood pressure (**Fig. 3**) increased from night to morning but decreased from morning to afternoon. For heart rate, only the linear component was statistically significant, indicating that a straight line best describes the data. The three group analysis for diastolic blood pressure resulted in a statistically significant effect for time, with both linear and quadratic components statistically significant. This means that the line from night to morning was significant and also the bend from morning to afternoon.

In the two group analysis, effects for both groups and time were statistically significant. The control group had significantly higher diastolic blood pressure than the hypertensives with diabetes, and the linear and quadratic components over time were both statistically significant.

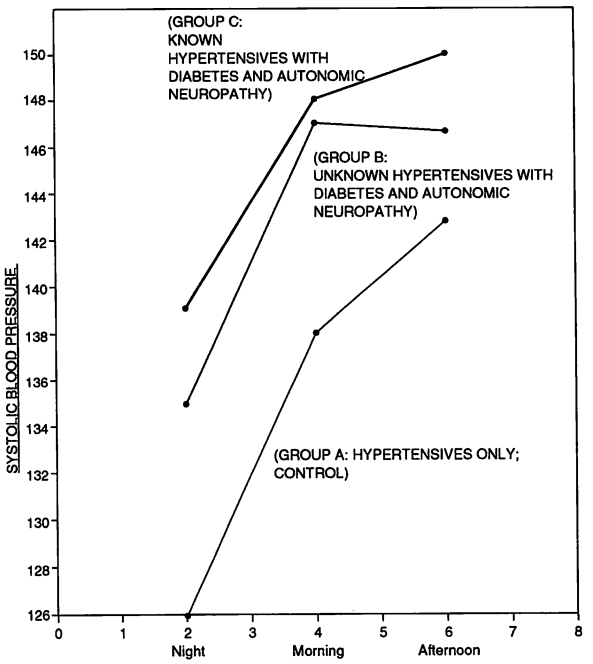

Fig. 1 Systolic blood pressure in patients with diabetes mellitus and autonomic neuropathy divided into known and unknown hypertension groups, and hypertensive patients (control group)

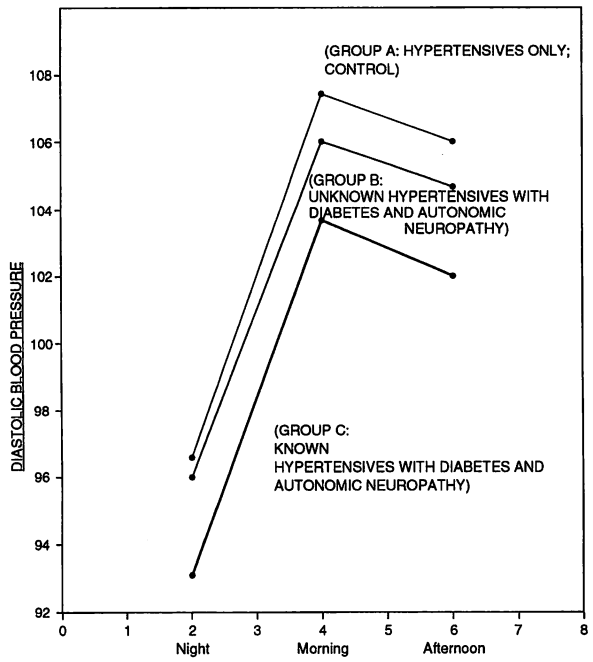

Fig. 2 Mean atrial pressure in patients with diabetes mellitus and autonomic neuropathy divided into known and unknown hypertension groups and hypertensive patients (control group)

DISCUSSION

Twenty-four hr ambulatory blood pressure monitoring detected hypertension in patients who had been treated for many years for diabetes only. This important finding indicates that diabetic patients with autonomic neuropathy may have associated hypertension which is only revealed by 24 hr ambulatory blood pressure monitoring. These patients ought to be treated accordingly.

Abnormal 24 hr blood pressure profiles have also occasionally been reported in patients who were not identified as having specific disorders of the autonomic nervous system, such as nondiabetic patients with essential hypertension, myocardial infarction, and other manifestations of coronary artery disease. It is of interest that the absence of the usual nocturnal blood pressure dip was associated with an increased prevalence of atherosclerotic cardiovascular complications in elderly patients and an increased frequency of stroke.

There is a reversal of circadian blood pressure rhythm not only in diabetics with autonomic failure but also in healthy shift workers[9]. Absence of the nocturnal decline in blood pressure occurs following cardiac transplantation[10]. A positive result of the Valsalva test has also been observed in patients with myocardial infarction and silent ischemia[11,12].

In our study, diabetic patients with autonomic neuropathy demonstrated the same circadian variation of blood pressure as the other groups. There was no significant difference in the 24 hr circadian

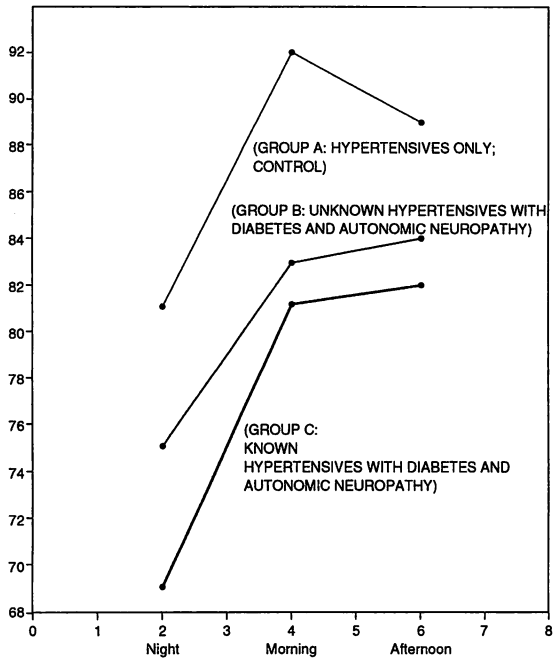

Fig. 3 Diastolic blood pressure in patients with diabetes mellitus and autonomic neuropathy divided into known and unknown hypertension groups and hypertensive patients (control group)

variation of the blood pressure and heart rate between patients receiving oral hypoglycemic and those receiving insulin (data not shown). Autonomic neuropathy causes impairment of parasympathetic function, and to a lesser degree, of sympathetic function. Among the clinical manifestations of autonomic malfunction are fixed heart rate, persistent tachycardia, and occasionally cardiac arrhythmias, denervation hypersensivity to cathecolamines, and blunted or absent response to beta-adrenergic blockade. It is plausible that in diabetic neuropathy denervation hypersensitivity to cathecholamine determines this particular pattern. Medical treatment seems to correct to a certain degree abnormalities in diabetic autonomic neuropathy.

Liniger *et al* found that 18 of 24 patients with diabetes had abnormal cardiovascular reflexes[13]. Nocturnal rise of blood pressure was observed in 6 patients only, blood pressure fell by 5 mmHg in 7, and 10 mmHg in the other 5. The nocturnal rise of blood pressure has been challenged by others[6]. However, amongst Liniger's patients with nocturnal rise of blood pressure, 4 patients had cardiovascular or renal events, and 3 died. No severe fatal or nonfatal event was reported in the group of patients in whom blood pressure fell markedly.

In our study there was no rise in nocturnal blood pressure. No fatal or nonfatal event was observed in any of our patients in 18–24 months of follow-up. Winocour and Anderson's patients, who showed no variations in the circadian rhythm of the blood pressure, may possibly have had similar clinical parameters to our patients[6].

The rise in the blood pressure in the early morning hours, contributing to the onset of myocardial infarction as reported by Muller *et al*[14] and discussed in the TIMI II study group, follows a pattern which was not different in our group of patients with diabetic neuropathy[15].

CONCLUSION

In conclusion, patients with diabetes and autonomic neuropathy demonstrate both microvascular as well as macrovascular complications. Studies have showed that nephropathy, retinopathy, cerebral vascular disease, and ischemic heart disease are exacerbated by hypertension and ameliorated by its treatment. Twenty-four hr ambulatory blood pressure monitoring is clinically useful in patients with diabetes and autonomic neuropathy in unmasking undetected hypertension. In our study of 19 patients with diabetes and autonomic neuropathy, 12 patients (66%), who were considered to be normotensive, were found to be hypertensive.

Patients with diabetes and autonomic neuropathy with a normal circadian pattern of blood pressure may have a better prognosis than patients with a nocturnal rise of blood pressure.

References

1) Pickering TG : Diurnal rhythms and other sources of blood pressure variability in normal and hypertensive subjects. *in* Hypertension (ed by Laragh JH, Brenner BM). Raven Press, New York, 1990; pp 1397–1405
2) Nakano S, Uchida K, Kigoshi T, Azukizawa S, Iwasaki R, Kaneko M, Morimoto S : Circadian rhythm of blood pressure in normotensive NIDDM subjects. Diabetes Care 1991; **8** : 707–711
3) Millar-Craig MW, Bishop CN, Raftery EB : Circadian variation of blood-pressure. Lancet 1978; **I** : 795–797
4) Mann S, Altman DG, Raftery EB, Bannister R : Circadian variation of blood pressure in autonomic failure. Circulation 1983; **68** : 477–483
5) Liniger C, Favre L, Adamec R, Pernet A, Assal J-Ph : Profil nycthemeral de la pression arterielle et de la frequence cardiaque dans la neuropathie diabetique autonome. Schweiz Wcshr 1987; **117** : 1949–1953
6) Winocour P, Anderson DC : The relationship between autonomic neuropathy and albumin excretion in insulin-treated diabetics (Let-

ter). Diabetic Med 1987; **4** : 265

7) Vaisrub S : Diabetes and the heart : The autonomic connection. *in* Diabetes and the Heart (ed by Zoneraich S). CC Thomas, Springfield ILL, 1978; pp 161–174
8) O'Brien E, Sheridan J, O'malley K : Dippers and non-dippers (Letter). Lancet 1988; **II** : 397
9) Sungberg S, Kohvakka A, Gordin A : Rapid reversal of circadian blood pressure rhythm in shift workers. J Hypertens 1988; **6** : 393–396
10) Reeves RA, Shapiro AP, Thompson ME, Johnsen A-M : Loss of nocturnal decline in blood pressure after cardiac transplantation. Circulation 1986; **73** : 401–408
11) Airaksinen KEJ, Koistinen MJ, Ikaheimo MJ, Pirttiaho H, Huikuri HV, Takkunen JT : Effect of coronary artery disease on parasympathetic cardiovascular reflexes in NIDDM patients. Diabetes Care 1990; **13** : 83–86
12) Airaksinen KEJ, Ikaheimo MJ, Linnaluoto MK, Niemela M, Takkunen JT : Impaired vagal heart rate control in coronary artery disease. Br Heart J 1987; **58** : 592–597
13) Liniger C, Favre L, Assal J-Ph : Twenty-four hour blood pressure and heart rate profiles of diabetic patients with abnormal cardiovascular reflexes. Diabetic Med 1991; **8** : 420–427
14) Muller JE, Tofler GH, Stone PH : Circadian variations and triggers of onset of acute cardiovascular disease. Circulation 1989; **79** : 733–743
15) Tofler GH, Muller JE, Stone PH, Forman S, Solomon RE, Knaterud GL, Braunwald E : Modifiers of timing and possible triggers of acute myocardial infarction in the thrombolysis in myocardial infarction phase II (TIMI II) study group. J Am Coll Cardiol 1992; **20** : 1049–1055