Relationship between serum parathyroid hormone levels in the elderly and 24 h ambulatory blood pressures

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Background **An association between serum parathyroid hormone (PTH) levels in normotensive elderly subjects and blood pressure values had been reported.**

Objective **To examine the relationship between PTH levels and other biochemical markers of calcium metabolism in elderly subjects and 24 h ambulatory blood pressures.**

Methods **We performed 24 h ambulatory blood pressure recordings for 123 independent elderly subjects aged 63–88 years using a SpaceLabs 90207 recorder. Mean night-time blood pressures were calculated from the average of readings during sleep; mean daytime blood pressures were calculated from the remaining recordings. Demographic data and details concerning the alcohol consumption and medication usage of the subjects were recorded. Serum PTH, 25-hydroxy-vitamin D, albumin, renin, aldosterone, noradrenaline, creatinine and calcium levels were measured.**

Results **Fifty-five patients were being administered antihypertensive therapy. Serum PTH levels correlated to the nocturnal systolic blood pressure (SBP; $\beta = 0.29$, $P = 0.002$), nocturnal diastolic blood pressure (DBP), daytime SBP and mean 24 h SBP on univariate and multivariate analysis. Aldosterone levels were related to nocturnal SBP in univariate analysis ($\beta = 0.21$, $P = 0.02$) but the relationship was weakened when PTH levels were included in the analysis ($\beta = 0.16$, $P = 0.09$). Nocturnal, daytime and mean 24 h blood pressures were not significantly related to serum calcium, 25-hydroxy-vitamin D, age, body mass index and alcohol consumption. Sex was a significant predictor of the DBP, men having higher levels than did women (daytime DBP $\beta = 0.29$, $P = 0.001$).**

Conclusions **Serum PTH levels are related strongly to the blood pressure, particularly the nocturnal blood pressure in the elderly. It is not known whether PTH levels are a consequence or a cause of the elevation in blood pressure.**

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Introduction

Parathyroid hormone (PTH) is a physiological regulator of calcium homeostasis involving bone and kidney [1]. Previous studies have shown that there is a relationship between PTH levels and hypertension, suggesting either that abnormalities in calcium metabolism are involved in the pathogenesis of hypertension or that an elevation in blood pressure leads to calciuresis and activation of calcium-regulatory hormones [2–5]. However, there are very few data concerning the relationship between calcium-regulatory hormones and hypertension in the elderly, for whom the pathogenesis of hypertension may differ from that of younger subjects and abnormalities of calcium metabolism are more likely to occur. We have examined the relationship between serum parathyroid hormone levels and other biochemical markers of calcium metabolism and the blood pressure for a group of healthy, elderly, community-dwelling subjects using 24 h ambulatory blood pressure monitoring.

Methods

We studied 123 free-living, independent, elderly community-dwelling volunteers, aged 63 years and more. Recruitment was from local retirement villages, church groups, bowling clubs and golf clubs. All of the patients gave their informed consent to participate in the study and the study had been approved by the South Eastern Sydney Area Ethics Committee. The subjects provided information on their medical history and were subjected to a medical examination by a qualified geriatrician (L.M.). Demographic data concerning alcohol consumption (subjects who consumed less than 10 g of alcohol per week were considered non-drinkers), cigarette consumption and the subject's medical history of diabetes, hyper-

tension, ischaemic heart disease, cardiac failure and osteoporosis were recorded. In addition, all medications being administered to the subjects, including vitamin supplementation and hormone-replacement therapy, were recorded. Patients with a history of myocardial infarction within the previous 12 months were excluded from the study. All of the subjects continued their current medications.

After subjects had rested supine for 15 min (between 0800 and 1000 h) venous blood was sampled, using a tourniquet, for determination of urea, creatinine, electrolytes, calcium, albumin, 25-hydroxy-vitamin D, PTH, plasma renin, aldosterone and noradrenaline levels. Total serum calcium and albumin levels were analysed spectrophotometrically on a Hitachi 747 analyser (Boehringer Mannheim, Castle Hill, Sydney, Australia). The serum total calcium level was measured and then a value for the free calcium level was derived by adding a correction factor (40 g/l minus the albumin level, multiplied by 0.02) to the total serum calcium level. The concentration of the intact PTH molecule was measured using the Biomediq Immulite chemi-luminescent EIA label (dioxetane; Biomediq DPC Pty Ltd, Doncaster, Victoria, Australia). 25-Hydroxy-vitamin D levels were determined by Incstar I125 radioimmunoassay (Stillwater, Minnesota, USA).

After the subjects had rested supine for 15 min, an office blood pressure reading was taken, after which a 24 h ambulatory blood pressure monitor (ABPM; SpaceLabs 90207; SpaceLabs Inc., Redmond, Washington, USA) was fitted to the subject. The ABPM was set to record the blood pressure at half-hourly intervals during the day and at hourly intervals from 2200 h to 0800 h. The sleeping time was taken as the time from when the subject went to bed until the subject awoke. Subjects were instructed to continue their usual daily activities whilst wearing the ABPM. During the next morning the ABPM was removed and data were downloaded into an IBM-compatible computer via the SpaceLabs data-interface unit. No manual editing of data was performed. Mean night-time blood pressures were calculated by averaging readings during sleep and mean daytime blood pressures by taking the mean of the remaining recordings. The following indices were derived from the ABPM data: average hourly systolic blood pressure (SBP) and diastolic blood pressure (DBP) recordings and mean 24 h, daytime and night-time SBP and DBP.

Statistical analysis was performed using the STATISTICA package [6]. Multiple linear regression was used to investigate relationships between the blood pressure, PTH level and other parameters. The regression results are expressed in terms of β (the average increase, i.e. the slope of the curve), the correlation coefficient (r) and the coefficient of determination (R^2) indicating the proportion of the variability in blood pressure explained by the fitted model. Analysis of variance was used to assess differences between hypertensives and normotensives. Values are expressed as means ± SD. $P < 0.05$ was considered statistically significant. χ^2 non-parametric testing was used for comparing binomial variables. The χ^2 statistic is expressed with one degree of freedom.

Results

All 123 subjects completed the study. The patients in the study were aged 63–88 years, with a median age of 72 years; 64% of the subjects were women. Of the subjects, 45% had a history of hypertension and 6% were diabetics; 3% were current smokers and 20% of the women were being administered oestrogen hormone-replacement therapy (Table 1). Three patients (2%) were being administered vitamin D orally and five subjects (4%) were being administered calcium supplementation. Only one patient with a history of hypertension was not being administered antihypertensive medication. One patient who had ambulatory blood pressure readings in the hypertensive range (mean 24 h blood pressure > 140/90 mmHg) had not had a prior history of hypertension. There were no significant differences between treated hypertensives and normotensives in sex, alcohol consumption and other cardiovascular risk factors. Of the total group, 59% were teetotal. Age and body mass index (BMI) values were significantly

Table 1 **Demographic data**

	All subjects (n = 123)	Hypertensives (n = 55)	Normotensives (n = 68)	Significance (*P*)
Age (years)	72.8 ± 4.9	73.7 ± 4.9	72.0 ± 4.7	0.049*
Men	44	18	26	0.52
Women	79	37	42	0.52
Body mass index (kg/m^2)	24.9 ± 3.2	25.5 ± 3.2	24.3 ± 3.2	0.04*
Hypertension	55			
Diabetes	7	5	2	0.14
IHD	7	4	3	0.50
Current smoker	4	3	1	0.2
Alcohol (g/week)	35 ± 71	33 ± 76	37 ± 68	0.76
HRT	16 (20% of the women)	7	9	0.78

Values are expressed as means ± SD. IHD, ischaemic heart disease; HRT, hormone-replacement therapy.
*Significance level defined as $P < 0.05$.

Table 2 **Mean blood pressure characteristics of normotensives and treated hypertensives**

	All subjects	Hypertensives	Normotensives	Significance (*P*)
Mean 24 h SBP (mmHg)	129 ± 14	135 ± 14	125 ± 12	< 0.01*
Mean 24 hr DBP (mmHg)	72 ± 9	73 ± 10	71 ± 7	0.07
Day SBP (mmHg)	133 ± 14	139 ± 14	129 ± 12	< 0.01*
Day DBP (mmHg)	75 ± 8	77 ± 9	74 ± 7	0.04*
Night SBP (mmHg)	117 ± 15	125 ± 15	111 ± 12	< 0.01*
Night DBP (mmHg)	63 ± 9	65 ± 10	61 ± 8	0.02*

Values are expressed as means ± SD. SBP, mean systolic blood pressure; DBP, mean diastolic blood pressure. *$P < 0.05$.

Table 3 **Biochemical values**

	All subjects	Hypertensives	Normotensives	Significance (*P*)
Noradrenaline (nmol/l)	4.13 ± 1.5	4.0 ± 1.5	4.3 ± 1.5	0.37
Plasma renin (pmol Al/ml/h)	6.4 ± 15.4	10 ± 22	3.2 ± 1.7	< 0.01*
Aldosterone (pmol/l)	356 ± 186	396 ± 218	324 ± 149	0.03*
Aldosterone : renin ratio	151 ± 178	153 ± 214	149 ± 143	0.89
Total calcium (mmol/l)	2.38 ± 0.10	2.37 ± 0.10	2.38 ± 0.10	0.68
Albumin (g/l)	41 ± 2	40 ± 3	41 ± 2	0.46
Free calcium	2.37 ± 0.09	2.36 ± 0.11	2.37 ± 0.09	0.88
Creatinine (mmol/l)	0.09 ± 0.02	0.10 ± 0.02	0.09 ± 0.01	0.02*
25-Hydroxy-vitamin D (nmol/l)	62 ± 22	66 ± 20	59 ± 23	0.09
Parathyroid hormone (pmol/l)	2.8 ± 1.2	2.9 ± 1.3	2.7 ± 1.1	0.41

Values are expressed as means ± SD. *$P < 0.05$.

Table 4 **Univariate analysis showing average increases in blood pressure per unit increase in serum parathyroid hormone level together with the associated significance and correlation coefficient**

	Average increase (β)	Significance (*P*)	Correlation coefficient (r)
Nocturnal SBP	0.25	< 0.01*	0.25
Nocturnal DBP	0.20	0.03*	0.20
Daytime SBP	0.20	0.03*	0.20
Daytime DBP	0.17	0.07	0.17
Mean 24 h SBP	0.22	0.02*	0.22
Mean 24 h DBP	0.14	0.13	0.14

SBP, systolic blood pressure; DBP, diastolic blood pressure. *$P < 0.05$.

Table 5 **Multivariate analysis showing average increases in blood pressure per unit increase in serum parathyroid hormone level adjusted for age, sex, body mass index, alcohol consumption and serum creatinine level, together with the associated significance and coefficient of determination**

	Adjusted average increase (β)	Significance (*P*)	Coefficient determination of (R^2)
Nocturnal SBP	0.29	< 0.01*	0.11
Nocturnal DBP	0.25	0.01*	0.13
Daytime SBP	0.22	0.02*	0.09
Daytime DBP	0.20	0.03*	0.17
Mean 24 h SBP	0.25	< 0.01*	0.10
Mean 24 h DBP	0.18	0.06	0.13

SBP, systolic blood pressure; DBP, diastolic blood pressure. *$P < 0.05$.

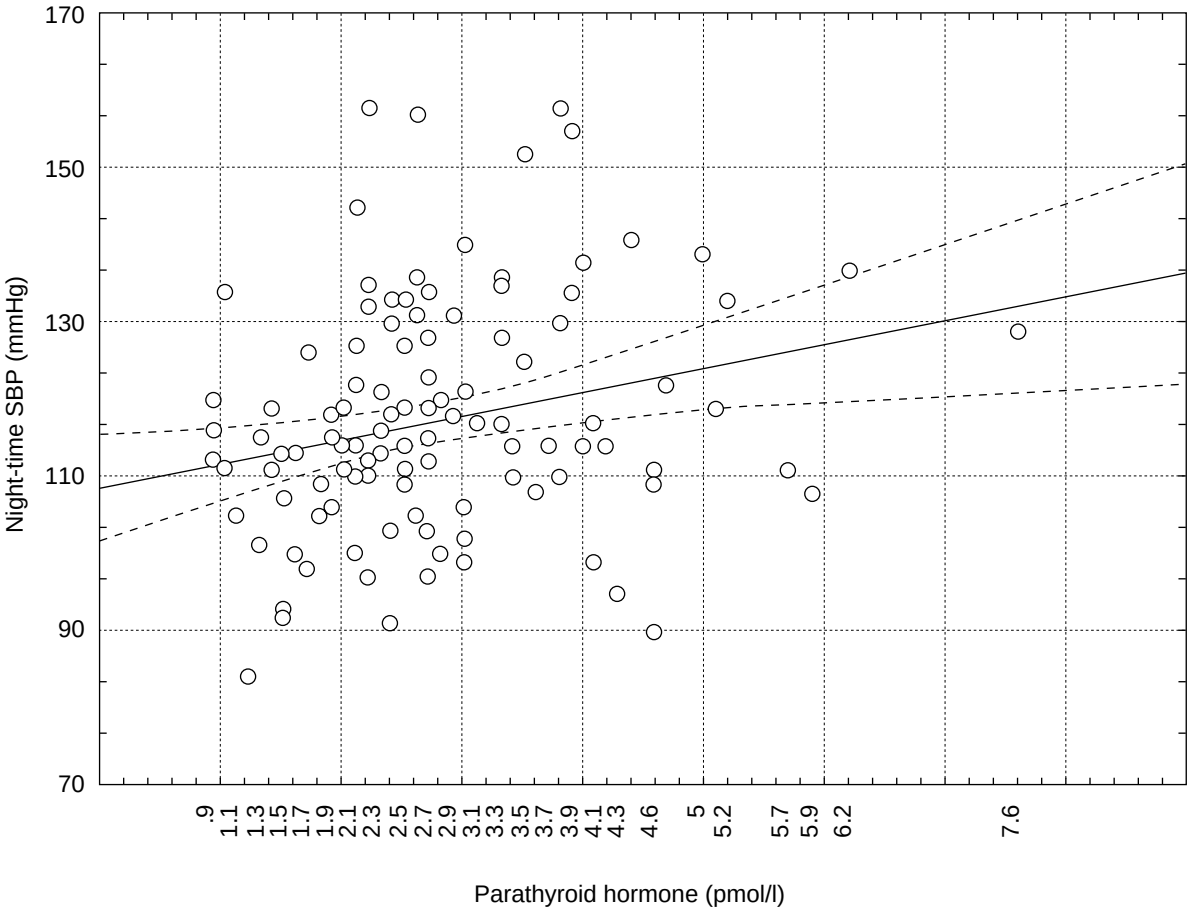
greater for the previously treated hypertensive subjects (Table 1).

The blood pressure parameters and differences between treated hypertensives and normotensives are shown in Table 2. Mean 24 h, daytime and night-time SBP were significantly higher for the treated hypertensive subjects than they were for the normotensive subjects. Mean daytime and night-time DBP were also significantly higher for the treated hypertensive subjects, but mean 24 h DBP did not differ significantly between the two groups.

The biochemical results for the subjects are shown in Table 3. PTH values were in the range 0.9–7.6 pmol/l. There was no significant difference between treated hypertensives and normotensives in serum PTH estimations; neither were there significant differences in noradrenaline, serum calcium, and 25-hydroxy-vitamin D levels. However, there were significant differences between hypertensives and normotensives in aldosterone levels, plasma renin activity and creatinine levels (Table 3), hypertensives having higher levels for each of these variables. Also, the PTH level was related to the serum creatinine level on linear regression ($\beta = 0.187$, $P = 0.04$).

On univariate analysis (Table 4, Fig. 1) serum PTH levels correlated strongly to nocturnal SBP ($\beta = 0.25$, $P = 0.007$) and to a weaker extent to nocturnal DBP ($\beta = 0.20$, $P = 0.03$), daytime SBP ($\beta = 0.20$, $P = 0.03$) and mean 24 h SBP ($\beta = 0.22$, $P = 0.02$; Table 4). Daytime DBP and mean 24 h DBP were not significantly related to PTH levels (daytime diastolic $\beta = 0.17$, $P = 0.07$; mean 24 h diastolic $\beta = 0.14$, $P = 0.13$). Using multivariate regression

Fig. 1



Univariate linear regression (—) with 95% confidence limits (- - -) for the relationship between the parathyroid hormone level and the nocturnal systolic blood pressure (SBP; $\beta = 0.25$, $P = 0.007$).

analysis, including the variables age, sex, BMI, serum creatinine level and alcohol consumption in the model (Table 5), the relationship between the serum PTH level and the blood pressure strengthened (nocturnal SBP $\beta = 0.29$, $P = 0.002$). When antihypertensive medication usage was added to the regression analysis the relationship of the PTH level with the blood pressure was not altered significantly (nocturnal SBP $\beta = 0.28$, $P = 0.002$, data not shown).

Serum calcium, free calcium, 25-hydroxy-vitamin D, plasma renin and creatinine concentrations, age and alcohol consumption were not related significantly to the nocturnal blood pressure, daytime blood pressure and mean 24 h blood pressure. The noradrenaline level was related to the nocturnal blood pressure (nocturnal DBP $P = 0.049$; nocturnal SBP $P = 0.03$). Sex was a significant predictor of an elevated diastolic blood pressure, men having higher mean 24 h DBP than did women ($\beta = 0.23$, $P = 0.01$). The BMI was not related significantly to the mean systolic ($\beta = 0.05$, $P = 0.61$) and diastolic blood pressures ($\beta = 0.15$, $P = 0.10$). Aldosterone levels were related significantly and positively to nocturnal SBP on univariate analysis ($\beta = 0.21$, $P = 0.02$) but the relationship was weakened when the PTH level was included in the analysis ($\beta = 0.159$, $P = 0.09$). The aldosterone : renin ratio was not related significantly to any blood pressure measurement.

The effect of antihypertensive medication usage on the biochemical parameters was also assessed (Table 6). Of the 55 hypertensive patients, all but one were being administered antihypertensive drugs, either singly or in combination. The drugs and total numbers of patients being administered them were angiotensin converting enzyme inhibitors (n = 25), calcium antagonists (n = 23), diuretics (n = 19), β-blocking agents (n = 7), prazosin (n = 2) and α-methyldopa (n = 2). Of the normotensive subjects, three were being administered β-blockers for prophylaxis of arrhythmia. Table 6 outlines the effect of the major classes of antihypertensive drugs on biochemical markers. PTH levels were not affected by anti-

Table 6 Effects of major types of medication on serum estimations of parathyroid hormone, renin, aldosterone, calcium and creatinine levels by analysis of variance (some patients were being administered a combination of several antihypertensive medications)

	Angiotensin converting enzyme inhibitors (n = 25)	Diuretics (n = 19)	Calcium antagonists (n = 23)
Parathyroid hormone (pmol/l)	3.1 ($P = 0.13$ NS)	2.57 ($P = 0.48$ NS)	3.0 ($P = 0.29$ NS)
Plasma renin (pmol Al/ml/h)	18.6 ($P = 0.00$)	11.2 ($P = 0.14$ NS)	7.4 ($P = 0.76$ NS)
Aldosterone (pmol/l)	307 ($P = 0.14$ NS)	467 ($P = 0.004$)	385 ($P = 0.04$ NS)
Aldosterone/renin	83 ($P = 0.03$)	142 ($P = 0.82$ NS)	113 ($P = 0.25$ NS)
Calcium (mmol/l)	2.37 ($P = 0.56$ NS)	2.39 ($P = 0.56$ NS)	2.37 ($P = 0.62$ NS)
25-Hydroxy vitamin D (nmol/l)	66.3 ($P = 0.25$ NS)	67.6 ($P = 0.23$ NS)	65.4 ($P = 0.39$ NS)
Creatinine (mmol/l)	0.10 ($P = 0.001$)	0.10 ($P = 0.12$ NS)	0.10 ($P = 0.08$ NS)

Values are expressed as means for each group. $P < 0.05$ was considered statistically significant. NS, not significant.

hypertensive medication usage. Aldosterone level estimations were increased significantly by diuretic usage ($P < 0.01$) and plasma renin and serum creatinine levels were increased by usage of angiotensin converting enzyme inhibitors ($P < 0.01$).

Discussion

In our study of healthy, independent, elderly, community-dwelling individuals serum PTH levels were related strongly to blood pressure measurements. The nocturnal blood pressure appeared to be related particularly strongly to serum PTH levels. These results suggest that PTH plays an aetiological role in hypertension in the elderly. Alternatively, increases in PTH levels may occur as a consequence of the elevation in blood pressure, particularly nocturnal blood pressure. This study extended the previous knowledge of the association of PTH levels with the blood pressure by studying both hypertensive and normotensive elderly subjects and by using ambulatory blood pressure monitoring, which provides more accurate and reliable measurements than do clinic blood pressure measurements alone [7]. In addition, we examined a number of possible predictors of blood pressures in the elderly using an ABPM. Very few data concerning predictors of the blood pressure for subjects in this age group using 24 h blood pressure recordings have been published.

Several studies have found relationships between hypertension and concentrations of PTH and vitamin D in middle-aged subjects. Young *et al.* [8] showed that the mean blood pressure in young hypertensive men was related to their PTH levels. Hvarfner *et al.* [2] found a weak relationship between the DBP in young untreated hypertensive subjects and their PTH levels using clinic blood pressures, but they found no such relationship for normotensives. However, Brickman *et al.* [9] showed that serum PTH levels correlated to clinic SBP and mean arterial pressures in normotensive subjects. Few data relating the blood pressure to PTH levels in older subjects have been published. St John *et al.* [10] have shown that there is a relationship between clinic blood pressure measurements and PTH levels in the elderly. By using an ABPM in our study of hypertensive and normotensive subjects we detected a stronger relationship between 24 h ambulatory blood pressure recordings and PTH levels in the elderly, particularly between PTH levels and the nocturnal blood pressure.

The nature of the relationship between the PTH level and the blood pressure is not known. Hypertension might cause an increase in calcium excretion, leading to an elevation in serum PTH concentrations and possibly a fall in bone mineral density. McCarron *et al.* [3] and St John *et al.* [10] postulated that patients with high blood pressures have a urinary calcium leak that lowers their calcium levels and stimulates a compensatory release of PTH. Evidence to support this hypothesis from our work is the relationship of the PTH level to the current blood pressure level rather than to a history of hypertension and the finding that mean PTH levels were not significantly higher in hypertensives. In our study, we observed a relationship between serum creatinine and PTH levels. However, the serum creatinine level does not appear to explain the strong relationship between the blood pressure and the PTH level, insofar as the addition of the creatinine level as a covariate did not alter the relationship between the blood pressure and PTH levels.

An inverse association between bone mineral density and the DBP has recently been reported for the elderly [11]. Those authors suggested that this relationship was due to chronic calciuresis associated with long-standing hypertension.

An alternative explanation for the relationship between the PTH level and the blood pressure is that elevated PTH levels or increased levels of a PTH hypertensive factor increase the blood pressure. The chronic infusion of PTH into normal human subjects has been shown to result in hypertension [12]. However, the experimental PTH levels used in that study were much higher than those found in members of our study population. The co-release together with PTH of a PTH hypertensive factor, namely a circulating substance discovered recently in the plasma of spontaneously hypertensive rats (SHR), which, when injected into normotensive rats, produces a

delayed hypertensive effect, could be another mechanism mediating an association between the PTH level and the blood pressure [13].

Chien *et al.* [14] reported that the administration of parathyroid calcium receptor agonist Norcalcin suppressed PTH levels and lowered the blood pressure in SHR, suggesting that a PTH hypertensive factor could be contributing to hypertension in SHR.

If the association between PTH levels in the elderly and their blood pressures is causative and related to calcium deficiency, then calcium supplementation would be expected to lower their blood pressures. Tagaki *et al.* [15] demonstrated that 4 weeks of oral calcium supplementation (1 g/day) suppressed serum PTH levels and reduced mean SBP and DBP in normocalcaemic elderly subjects aged 65–86 years with untreated essential hypertension. However, another study found no significant effect of calcium supplementation in lowering blood pressures in subjects aged 50–80 years [16]. Other studies of calcium supplementation have detected little or no effect on blood pressures in younger patients [17–19].

Our study provides information about predictors of the blood pressure in the elderly when 24 h ambulatory blood pressure monitoring is performed. Interestingly, we found no association between age, weight and alcohol consumption and ambulatory blood pressure recordings. The small age range of our subject group and also the fact that relatively few subjects in the group consumed alcohol regularly may have affected our ability to detect an association of these factors with the blood pressure. We did, however, find a relationship between the BMI and the DBP among men. Our inability to confirm that there was an association among the traditional predictors of blood pressure using an ABPM is in accord with the results of a study by Staessen *et al.* [20], who showed that the 'well-established' relations of the SBP and DBP to age and BMI are overestimated by conventional sphygmomanometry.

A limitation of our study was that we allowed our previously hypertensive patients to continue their antihypertensive medication. This might have reduced the association between the blood pressure and the PTH level. Also, a small proportion of our subjects were being administered vitamin D or calcium supplements, or both, but this probably did not affect the results substantially. The use of single PTH-level measurements rather than repeated measurements might have weakened the correlation to the blood pressure by introducing greater variability. Finally, we did not measure the serum free calcium level directly from freely flowing blood, but instead derived a value from the total calcium level, corrected for the prevailing albumin value. This method might have affected our inability to find any significant correlations among calcium, PTH and 25-hydroxy-vitamin D levels.

In conclusion, we have shown that there is a strong correlation between serum PTH levels in the healthy elderly and their ambulatory blood pressures, particularly the nocturnal SBP but also the nocturnal DBP and daytime SBP and DBP. It is not known whether elevated PTH levels are related causally to the increased blood pressures or are a secondary phenomenon. Further studies of calcium and vitamin D supplementation are required in order to clarify the relationship between the PTH level and the blood pressure in the elderly.

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