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Original Article

Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure

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Abstract

Background. Left ventricular hypertrophy (LVH) is both common and an important predictor of risk of death in end-stage renal failure (ESRF). In mild to moderate chronic renal failure (CRF), the timing of onset of LVH and the factors involved in its initial development have not been fully elucidated. The present study was undertaken to examine the prevalence and potential determinants of echocardiographically determined LVH in this connection, and to compare 24-h ambulatory blood pressure (BP) recordings with BP measured at a previous clinic visit.

Methods. From a cohort of 120 non-diabetic patients who had been attending a nephrology clinic, 118 agreed to participate in the study. Of these we selected for analysis 85 stable patients (37 male). Patients with known cardiovascular disease, those with a history of poor compliance with antihypertensive medication, and those in whom such medication had been changed in the previous 3 months were excluded. Clinic BP, 24-h ambulatory BP, echocardiography, body mass index (BMI), serum creatinine (SCr), creatinine clearance (CrCl), haemoglobin (Hb), fasting cholesterol (CHOL), triglyceride TRlGL), plasma glucose, calcium (Ca), phosphate (PO_4), alkaline phosphatase (ALK PHOS), parathyroid hormone (PTH) concentrations, and 24-h urinary protein were assessed in all patients. Seventy-seven per cent were on antihypertensive medication.

Results. LVH was detected in 16% of patients with CrCL >30 ml/min, and 38% of patients with CrCl <30 ml/min. By stepwise regression analysis, ambulatory systolic BP ($P<0.0001$), male gender ($P<0.0001$), BMI ($P<0.0002$), and Hb concentration ($P<0.002$) were the only independent determinants of left ventricular (LV) mass. Nocturnal systolic BP ($P<0.02$) was the main determinant of LVH in the group of patients with advanced CRF. The correlation between left ventricular mass index (LVMI) and mean 24-h ambulatory systolic BP ($r=0.52$, 95% confidence interval 0.50–0.54) was statistically significantly stronger than with outpatient systolic BP ($r=0.25$, 95% confidence interval 0.23–0.27). The same was true for the correlation between LVMI and mean 24-h ambulatory diastolic BP ($r=0.42$, 95% confidence interval 0.40–0.44), and outpatient diastolic BP ($r=0.22$, 95% confidence interval 0.20–0.24).

Conclusions. Twenty-four hour ambulatory BP recording and echocardiography are required for accurate diagnosis of inadequate BP control and early LVH in patients with chronic renal impairment, independent determinants of which are hypertension, male sex, BMI, and anaemia.

Key words: ambulatory blood pressure (BP); anaemia; chronic renal failure (CRF); hypertension; left ventricular hypertrophy (LVH)

Introduction

Cardiovascular disease is the leading cause of death in patients on renal replacement therapy [1–3]. Left ventricular hypertrophy (LVH) is a strong predictor of myocardial infarction, cardiac failure, sudden death, and stroke in patients with essential hypertension and normal renal function and those with end-stage renal disease (ESRD) [4–7]. LVH is common in ESRD and frequently predates the initiation of dialysis treatment [7–9], suggesting that the factors responsible may be present in early renal impairment. Information regarding the stage of renal impairment at which LVH occurs, the important factors involved in its initial development, and optimum monitoring and management are scant.

A number of factors potentially affecting cardiovascular outcome have been postulated or defined in patients with ESRD [3,7–14], but these have not been assessed thoroughly in moderate renal impairment. The 24-h ambulatory BP profile in patients with CRF, those on haemodialysis, and renal transplant recipients differs from that in most essential hypertensives in that nocturnal fall in BP is frequently reduced in these

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patients [15,16]. The significance of this in patients with moderate renal impairment has not been fully assessed.

We have analysed the relationship between 24-h ambulatory BP profile and other possible risk factors, and LVH in patients with less severe renal impairment than have hitherto been studied in depth.

Methods

From a cohort of 120 non-diabetic patients who had been attending a nephrology clinic, 118 agreed to participate in the study. Of these, we selected for analysis 85 subjects, 37 male and 48 female, mean age 49 (SD 14) years, mean CrCl 39 (SD 30) ml/min. We excluded from analysis patients with known cerebrovascular, peripheral vascular, cardiac valvular, or coronary disease, those with a previous hitory of poor compliance with antihypertensive drug treatment and those in whom such treatment had been altered during the preceding 3 months. All patients studied were clinically and biochemically stable. Seventy-seven per cent of patients were receiving antihypertensive treatment. Fourteen per cent were Afro-Caribbean, and 13% were smokers. Fifteen patients had polycystic kidney disease and seven had reflux nephropathy. Remaining patients had biopsy-proven glomerulonephritis (15), interstitial nephritis (13), focal segmental glomerulosclerosis (6), vasculitis (7), hypertensive nephropathy (4), and other diagnoses (3). In 15 patients the renal diagnosis was unknown. The population was divided into two groups according to the CrCl level: group 1: >30 ml/min ($n=43$), and group 2: <30 ml/min ($n=42$).

BMI, CrCl, 24-h urinary protein (U Prot) excretion, fasting CHOL, TRIGL, plasma glucose, Hb, albumin, total Ca, PO_4, ALK PHOS, and PTH (IRMA 2-site chemiluminescence assay for intact PTH (Ciba–Corning)) levels were measured on the day of the study and the results were compared with computer-stored previous laboratory data.

Groups 1 and 2 patients were similar in age and BMI. Levels of CHOL, TRIGL, ALK PHOS, and Ca were also similar in the two groups. Degree of proteinuria, PO_4, and PTH (upper limit of normal 5–4 pmol/l) were significantly lower, and Hb concentration significantly higher in group 1 compared to group 2 (Table 1). Single supine or sitting BP measurements recorded at the clinic visit preceding the study were used for analyses. The year of onset of hypertension and the drug treatment were also recorded. Patients were categorized according to the number and type of antihypertensive agents, i.e. diuretics, beta-adrenoreceptor blockers, calcium-channel blockers, ACE inhibitors and others.

BP (Spacelabs 90207) was recorded every half hour between 0700 and 2200 hours (daytime), and hourly between 2200 and 0700 hours (night-time). The mean 24-h daytime and night-time BP for both systolic (sBP) and diastolic (dBP) BP, and BP dipping, were calculated. Calculations were also made of values during 'awake' and 'sleep' periods. As there were no significant differences between these values and mean daytime and night-time BP values, the latter were used for analysis. Dipping was defined as a reduction in night-time mean arterial pressure greater than 10% of the daytime mean arterial pressure [17]. Duration of hypertension was greater in group 2 (Table 1). Clinic and ambulatory systolic BP levels were significantly higher in group 2. There was no significant difference in the levels of clinic or ambulatory diastolic BP between the groups.

Two-dimensionally guided M-mode echocardiography (Acuson) was performed by one experienced observer (MG), unaware of other results, according to the recommendations of the American Society of Echocardiography (ASE) [18]. Interventricular septum thickness (IVS), posterior left ventricular wall thickness (PLVW), end-diastolic (LVEDD), and end-systolic (LVESD) left ventricular internal dimensions were measured. LV dilatation was defined as LVEDD >5.6 cm. Left ventricular mass (LVM) was determined by the equation developed by Devereux *et al.* [19]:

$$LVM_{(ASE)} = 0.8 \times 1.04\,[(IVS + LVEDD = PLVW)^3 - LVEDD^3] + 0.6 \text{ g}$$

Left ventricular mass index (LVMI) was calculated by dividing LVM by body surface area. To determine the prevalence of LVH, sex-specific criteria were used [20]: (men LVMI >131 g/m^2; women LVMI >100 g/m^2). Relative wall thickness (RWT), a measure of left ventricular geometry, was

Table 1. Clinical characteristics of the two groups (mean $\pm$ SD)

	Group 1	Group 2	*P*
Gender (M/F)	23/20	14/28	
Age (years)	46 $\pm$ 11	52 $\pm$ 16	n.s.
BMI (kg/m^2)	26 $\pm$ 4	26 $\pm$ 4	n.s.
SCr (μmol/l)	155 $\pm$ 57	509 $\pm$ 235	<0.00001
U prot (g/24 h)*	0.44 (0.01–3.5)	1.5 (0.17–16.8)	<0.0006
Hb (g/dl)	13.7 $\pm$ 1.2	10.9 $\pm$ 18	<0.00001
Ca (mmol/l)	2.24 $\pm$ 0.10	2.28 $\pm$ 0.13	n.s.
PO_4 (mmol/l)	1.08 $\pm$ 0.16	1.65 $\pm$ 0.44	<0.00001
PTH (pmol/l)*	5.5 (1.5–22)	14.4 (1.1–124)	<0.00002
Duration of hypertension (years)*	5 (0–18)	6.5 (0–28)	<0.05
Clinic sBP (mmHg)	138 $\pm$ 23	150 $\pm$ 21	<0.03
Clinic dBP (mmHg)	88 $\pm$ 14	87 $\pm$ 13	n.s.
24-h sBP (mmHg)	130 $\pm$ 14	138 $\pm$ 13	<0.008
24-h dBP (mmHg)	84 $\pm$ 9	85 $\pm$ 8	n.s.
Night sBP (mmHg)	121 $\pm$ 15	132 $\pm$ 17	<0.003
Night dBP (mmHg)	76 $\pm$ 11	78 $\pm$ 11	n.s.
LVMI (g/m^2) (M)	108 $\pm$ 22	118 $\pm$ 21	n.s.
(F)	86 $\pm$ 17	101 $\pm$ 26	<0.03

*Median and range.

calculated as:

$$RWT = (2\ PLVW)/LVEDD$$

Concentric hypertrophy was defined as RWT > 0.45 in the presence of LVH, eccentric hypertrophy as RWT < 0.45 in the presence of LVH. Fractional shortening (FS), a measure of left ventricular function, was calculated as:

$$FS(\%) = (LVEDD - LVESD) \times 100/LVEDD$$

Systolic dysfunction was defined as FS < 25%.

Computer analyses were performed using Statgraphics version 4.0 by the Statistical Graphics Corporation, copyright 1989. Comparisons between the groups were made using paired *t* tests for parametric data, and Wilcoxon's tests for non-parametric data. Pearson correlation coefficients and stepwise multivariate regression analyses were used to identify the possible determinants of LVMI. Stepwise multiple linear regression was carried out using LVMI as the dependent variable, and gender, age, SCr, U Prot, Hb, PTH, 24-h sBP, 24-h dBP, daytime and night-time systolic and diastolic pressures, systolic and diastolic BP dipping, clinic sBP, and clinic dBP as the independent variables. Since the order of addition, or deletion, of the variables from the stepwise regression influences the significance of the other variables, the initial model was optimized by best subset regression to select the first seven variables giving the highest *r* value.

Results

Hypertension (mean 24-h sBP > 140, mean 24-h dBP > 90 mmHg) despite treatment, was present in 11 patients in group 1 (26%) and 17 patients in group 2 (46%). In the majority, the degree of hypertension was mild, i.e. sBP < 160 mmHg, dBP < 100 mmHg. In group 1, 26% of patients were normotensive, 30% were on one antihypertensive agent, 35% were on two or more agents, and 9% were untreated hypertensives. In group 2, 7% of patients were normotensive, 28% were on one antihypertensive agent, 60% were on two or more agents, and five were untreated hypertensives.

Forty per cent (17/43) of group 1 and 52% (22/42) of group 2 patients were categorized as non-dippers. The loss in physiological night-time BP was observed in hypertensive patients, regardless of whether BP was poorly or well controlled, but not in normotensive subjects. There was no association between non-dipper status and number or type of antihypertensive agents.

The prevalence of LVH was 16% in group 1 and 38% in group 2. Half the patients with advanced renal failure (CrCl < 10 ml/min) had LVH. The percentage of concentric LVH was 7 and 26% in groups 1 and 2 respectively. LV dilatation also increased with progression of renal failure from 9% in group 1 to 17% in group 2. Systolic function was preserved in all but one patient in group 2.

A highly significant positive correlation was found between LVMI and mean ambulatory systolic ($r = 0.52$, $P < 0.001$) and diastolic ($r = 0.42$, $P < 0.0001$) pressures (Figure 1). Correlations with mean clinic systolic ($r = 0.25$, $P < 0.03$) and diastolic ($r = 0.22$, $P < 0.05$) pressures were significant but less strong. There was a significant difference between the correlation coefficients for the relationship between LVMI and mean ambulatory systolic pressure ($r = 0.52$, 95% confidence interval 0.50–0.54), and for clinic sBP and LVMI ($r = 0.25$, 95% confidence interval 0.23–0.27). The same is true for the correlations between mean 24-h dBP and LVMI ($r = 0.42$, 95% confidence interval 0.40–0.44) and for the clinic dBP and LVMI ($r = 0.22$, 95% confidence interval 0.20–0.24). The fact that confidence intervals for the two slopes do not overlap indicates that the difference in slopes is highly statistically significant.

Night-time BP was a particularly strong univariate correlate of LVMI in patients in group 2: $r = 0.64$, $P < 0.0001$ for sBP and $r = 0.55$, $P < 0.0002$ for dBP. A significant negative correlation between LVMI and BP dipping was found in group 2 only: $r = -0.51$, $P < 0.0001$ for sBP dip and $r = -0.43$, $P < 0.005$ for dBP dip. There was no significant relationship between duration of hypertension or hypertensive drug regime and LVMI.

LVMI was positively associated with SCr ($r = 0.28$, $P < 0.01$) and inversely related to Hb concentration ($r = -0.28$, $P < 0.01$) in groups 1 and 2 combined. In group 2 alone a significant negative correlation was found between Hb and LVMI ($r = -0.44$, $P < 0.004$). Other significant associations of LVMI were U Prot output ($r = 0.25$, $P < 0.03$), PTH ($r = 0.23$, $P < 0.004$), and age ($r = 0.21$, $P < 0.05$). No significant association was found between LVMI and underlying renal disease, serum Ca, PO_4 and serum $CaPO_4$ product, ALK PHOS, CHOL, or TRIGL levels. A significant correlation was found between LVM and BMI ($r = 0.40$, $P < 0.002$). A significant association was found between BMI and sBP dip ($r = -0.37$, $P < 0.02$).

Independent determinants of LV mass

By stepwise multiple regression analyses, male gender, BMI, ambulatory sBP, and Hb concentration were the only independent determinants of LVM and together explained 58% of the variability in the whole population. Daytime sBP was the main BP determinant of LVM in patients in group 1. Night-time sBP was the most important determinant of LVM in group 2. (Table 2).

Discussion

None of our patients had clinical evidence of cardiac disease, and our results confirm the importance of echocardiography in making an early diagnosis of LVH. We found that LVH, which identifies patients at risk of cardiac death and stroke [4,7], increases with progression of renal failure and is particularly common in patients with advanced CRF. The incidence of LV dilatation, also a marker of poor prognosis in uraemic patients [21], increases with the degree of renal impairment. Systolic dysfunction appears to be a late event in renal failure.

Our results confirm the superiority of 24-h ambulatory BP monitoring in establishing or refuting the

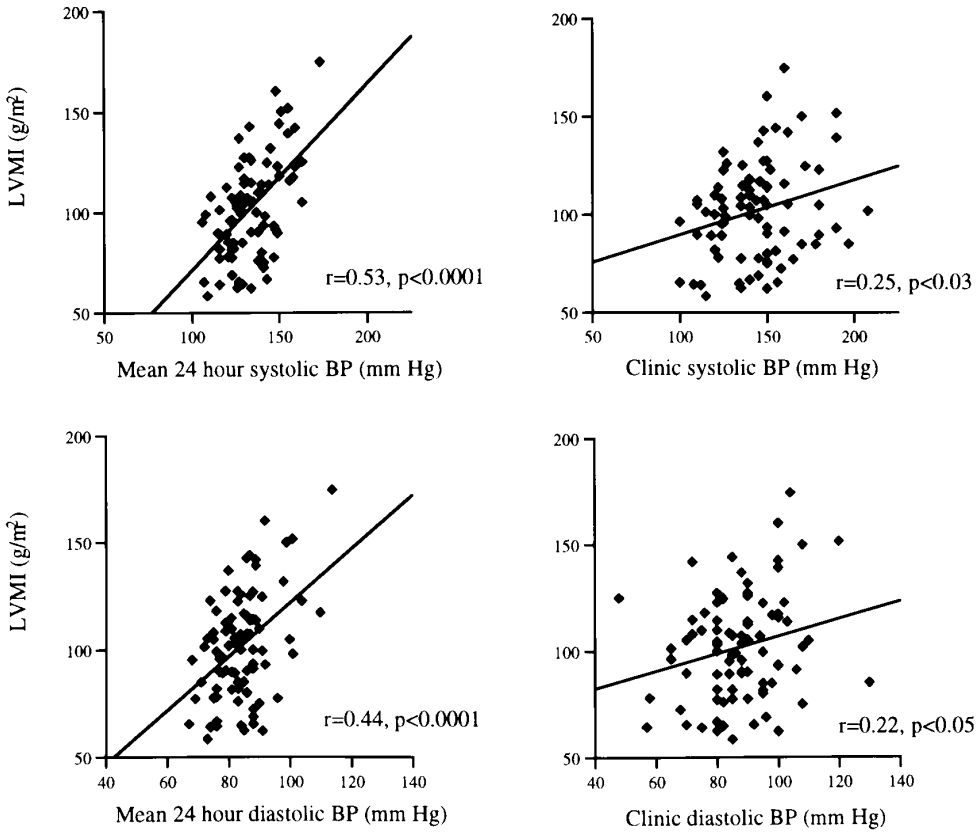

Fig. 1. Correlation between mean 24-h systolic and diastolic, clinic systolic and diastolic BP, and LVMI in groups 1 and 2 combined. Note much closer correlations between mean ambulatory BP and LVMI.

Table 2. Risk factors for LVH (stepwise multiple regression for LVM)

Step	Predictors	R^2 (%)	*P*
Groups 1 and 2			
1	Male gender	0.29	<0.0001
2	Male gender, BMI	0.43	<0.0002
3	Male gender, BMI, 24-h sBP	0.54	<0.0001
4	Male gender, BMI, 24-h sBP, Hb	0.58	<0.002
Group 1			
1	Male gender	0.34	<0.0001
2	Male gender, BMI	0.50	<0.0001
3	Male gender, BMI, day sBP	0.62	<0.0006
4	Male gender, BMI, day sBP, Hb	0.67	<0.03
Group 2			
1	Night sBP	0.32	<0.02
2	Night sBP, male gender	0.49	<0.0002
3	Night sBP, male gender, Hb	0.54	<0.007
4	Night sBP, male gender, Hb, BMI	0.61	<0.02

presence of significant hypertension (despite treatment) when compared with casual single outpatient clinic recordings. In our cohort of patients, ambulatory BP correlated more closely with LVH than clinic BP, as has been widely reported in non-renal hypertensive subjects [5,16,21].

We also confirm that absence of nocturnal decline in blood pressure is common in moderate to severe renal impairment [15]. It has recently been shown that cardiovascular morbidity is increased in hypertensive subjects with a blunted nocturnal fall in BP [22]. The reduction in nocturnal BP dip is associated with BMI in patients with advanced CRF, a connection which may be explained by volume overload. However, we did not determine the contribution of chronic volume overload, adiposity, and lean mass to BMI. Increased BMI is an important risk factor for LVH. In the Framingham population-based study [23], LV mass has been found to be related to obesity regardless of its hypertensive effect.

Anaemia is also a determinant of LVH in pre-ESRD as has been previously shown in dialysis patients [12]. None of the other variables we studied proved to be independent predictors of LVH, but all were found in association with higher mean sBP in the patients with advanced CRF. This may account for the fact that such factors have previously been postulated as determinants of LVH in dialysis patients [9,24]. Although the prevalence of LVH increases with progression of renal failure, we did not demonstrate that SCr concentration *per se* is an independent contributor to alteration in cardiac anatomy.

The factors we describe do not account in full for all the variability in LV mass observed. Whether previous hypertension, no longer present at the time of our study, accounts for this discrepancy or whether other factors, unidentified to date, are relevant is unknown.

It has been shown that cardiac hypertrophy can be reversible in essential hypertension by improved BP control and that changes in LVM during treatment predict subsequent cardiovascular outcome [6]. Amelioration of anaemia with erythropoietin has also been shown to reduce cardiac mass in some dialysis patients [13]. If LVH in CRF reflects the additive effects of hypertension, increased BMI, and anaemia, the extent to which correcting these conditions can reduce the cardiac abnormalities and their ensuing complications in CRF needs to be determined by follow-up studies.

It is clear that single outpatient BP recordings at infrequent intervals provide a most incomplete picture of BP control in patients with renal impairment, and that LVH is common in pre-ESRD and may be missed unless echocardiography is carried out. The levels of BP found in our patients are likely representative of patients with chronic renal impairment as a whole, and the relatively high prevalence of LVH we have found suggests—although it does not prove—that this degree of BP control may be inadequate to prevent LVH or cause it to regress. A more rigorous approach to BP control on the part of the clinician, with 24-h BP monitoring, regular echocardiography, correction of anaemia (with erythropoietin if necessary), and maintenance of ideal body weight, may be required—at least in patients with moderate to severe renal impairment—if optimal management is to be achieved. It has not escaped our notice that major logistic and cost implications are involved.

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References

1. Raine AEG, Magreiter R, Brunner FP *et al*. Report on management. of renal failure in Europe, XXII, 1991. *Nephrol Dial Transpantl* 1992; 7 [Suppl 2]: 7–35
2. Consensus Development Conference Panel. Morbidity and mortality of renal dialysis. An NIH Consensus Conference Statement. *Ann Intern Med* 1994; 121: 62–70
3. Kjellstrand CM, Hylander B, Collins AC. Mortality on dialysis. On the influence of early start, patients' characteristics, and transplantation and acceptance rates. *Am J Kidney Dis* 1990; 15: 483–490
4. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiography determined left ventricular mass in the Framingham heart study. *N EngI J Med* 1990; 322: 1561–1566
5. Pickering TG. Ambulatory monitoring and blood pressure variability. London, Science Press, 1991; Ch 13; 1–15
6. Devereux RB, de Simone G, Ganau A, Roman MJ. Left ventricular hypertrophy and geometric remodelling in hypertension: stimuli, functional consequences and prognostic implications. *J Hypertens* 1994; 12 [Suppl 10]: 117–127
7. Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end stage renal disease. *Kidney Int* 1989; 36: 286–290
8. Foley RN, Parfrey PS, Harnett JD *et al*. Clinical and echocardiographic disease in patients starting end stage renal disease therapy. *Kidney Int* 1995; 47:186–192
9. Greaves SC, Gamble GD, Collins JF, Whalley GA, Sharpe DN. Determinants of left ventricular hypertrophy and systolic dysfunction in chronic renal failure. *Am J Kidney Dis* 1994; 24: 768–776
10. Timio M, Lippi G, Venanzi S, Verdura C, Monarca C. Clinical aspects of left ventricular hypertrophy in uremia.In: Timio M, Wizemann V, Venanzi S, eds. *Cardionephrology 3.* Consenza, Editoriale Bios, 1995; 331–336
11. Ma KW, Green EL, Raij L. Cardiovascular risk factors in chronic renal failure and hemodialysis populations. *Am J Kidney Dis* 1992; 19: 505–513
12. Silberberg JS, Rahal DP, Patton R, Sniderman AD. Role of anemia in the pathogenesis of left ventricular hypertrophy in end stage renal disease. *Am J Cardiol* 1989; 64: 222–224
13. Macdougall IC, Lewis MP, Saunders MJ *et al*. Long term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin. *Lancet* 1990; 335: 489–493
14. Harnett JD, Kent GM, Barre PE, Taylor R, Parfrey PS. Risk factors for the development of left ventricular hypertrophy in a prospectively followed cohort of dialysis patients. *J Am Soc Nephrol* 1994; 4:1486–1490
15. Baumgart P, Walger P, Gemen S, von Eiff M, Raidt H, Rahn KH. Blood pressure elevation during the night in chronic renal failure, hemodialysis and after renal transplantation. *Nephron* 1991; 57: 293–298
16. Lipkin GW, Tucker B, Giles M, Raine AEG. Ambulatory blood pressure and left ventricular mass in cyclosporin–and non-cyclosporin-treated renal transplant recipients. *J Hypertens* 1993; 11: 439–442
17. Verdecchia P, Schillaci G, Porcellati C. Dippers versus non-dippers. *J Hypertens* 1991; 9 [Suppl 8]: S42–S44
18. Sahn DJ, De Maria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58: 1072–1083
19. Devereux RB, Alonso DR, Lutas EM *et al*. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; 57: 450–458
20. Levi D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham study. *Am J Cardiol* 1987; 59: 956–960
21. London GN, Fabiani F, Marchais SJ *et al*. Uremic cardiomyopathy: an inadequate left ventricular hypertrophy. *Kidney Int* 1987; 31: 973–980
22. Verdecchia P, Porcellati C, Schillaci G *et al*. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; 24: 793–801
23. Mancia G. Ambulatory blood pressure monitoring: research and clinical applications. *J Hypertens* 1990, 8 [Suppl 7]: S1–S13
24. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. *JAMA* 1991; 226: 231–236

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