Kidney International, Vol. 58 (2000), pp. 260–268

Inadequate diagnosis and therapy of arterial hypertension as causes of left ventricular hypertrophy in uremic dialysis patients

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Inadequate diagnosis and therapy of arterial hypertension as causes of left ventricular hypertrophy in uremic dialysis patients.

Background. Left ventricular hypertrophy (LVH) is highly prevalent in the dialyzed population, possibly because of inadequate diagnosis and therapy of arterial hypertension. The purpose of this study was to ascertain the adequacy of our approach in correctly identifying and treating arterial hypertension in our dialysis center.

Methods. Fifty-five dialyzed uremics were studied by continuous ambulatory blood pressure (BP) monitoring, which started before a single hemodialysis (HD) session, continued for 24 hours after HD ended, and was repeated for 15 minutes before the beginning of the next HD. Clinical pre-HD and post-HD routine BP measurements taken the month preceding BP monitoring were retrieved, and echocardiography was performed.

Results. LVH was present in 46 out of 55 patients, and clinical pre-HD arterial hypertension was present in 36 out of 55. There were discrepancies between clinical and monitored BPs, mostly concerning diastolic pre-HD BP since BP readings were lower than monitored BP records ($P < 0.0002$). Although both clinical and monitored BPs bore strong direct correlations with the left ventricular mass (LVM), the closest correlations were those for monitored BP. Four groups of patients were identified by BP monitoring: group A ($N = 14$), with persistently normal BP, and group D ($N = 13$), with persistently supranormal BP levels. There were also two other groups (group B, $N = 19$; and group C, $N = 9$), whose BP values were high before HD, normalized after HD, and then increased again either soon after HD (group C) or later on following HD (group B). Monthly averaged clinical pre-HD mean BP values differed significantly among the four groups [91 ± 10 (SD) mm Hg in group A, 101 ± 7 in group B, 106 ± 6 in group C, and 106 ± 7 in group D; $P < 0.0001$, analysis of variance], as did their corresponding LVMs [132 ± 27 g/m^2 body surface area (BSA), 156 ± 26, 201 ± 51, and 200 ± 36; $P < 0.0001$]. There were also differences in dialytic age, which was significantly longer in group A patients (109 ± 54 months), who also tended to have higher, although not significantly higher, Kt/V_{urea} values. No differences, however, were detected among the groups as far as type, dosages, and number of antihypertensive drugs given to each individual patient.

Conclusions. The high prevalence of LVH in the dialysis population might be the result of inadequate diagnosis and therapy of arterial hypertension. Arterial hypertension, in fact, was insufficiently treated in our dialysis center, since patients with varying degrees of severity of both arterial hypertension and LVH were kept on antihypertensive therapy of similar strength. Undertreatment may have resulted from not having recognized and/or from having underestimated the severity of arterial hypertension since some clinical BPs were measured incorrectly. Reluctance to use more aggressive antihypertensive therapy might also result from the deceptive feeling of "normalized" BP that one has following volume unloading with dialysis. This causes both the BP to run out of control between dialyses and LVH to worsen.

Key words: antihypertensive therapy, LVH, chronic uremia, cardiovascular mortality, blood pressure.

Received for publication May 26, 1999
and in revised form January 25, 2000
Accepted for publication February 2, 2000

Left ventricular hypertrophy (LVH) is the single strongest predictor of adverse cardiovascular events [1, 2]. Besides the subject's age, arterial hypertension is the closest clinical correlate to LVH both in uremic patients and in the general population as well [3, 4]. Over the last few years, the increased use of powerful antihypertensive drugs has resulted in a reduced prevalence of arterial hypertension and a concomitant decline in LVH and cardiovascular mortality in the general population [5]. The cardiovascular death rate, however, remains persistently elevated in dialysis patients [6, 7], while both arterial hypertension and LVH are still highly prevalent [8, 9]. Studies on dialysis patients, however, have shown that LVH is potentially reversible when a good dialysis regimen is combined with aggressive anti-

hypertensive treatment [10]. Thus, inadequate diagnosis and therapy of arterial hypertension may be likely causes for LVH being so highly prevalent in uremic patients. The purpose of this study was to ascertain the adequacy of our current approach in identifying and treating arterial hypertension in our center. In this study, we have collected indicators that may help explain why arterial hypertension in dialysis patients might remain both underdiagnosed and undercured.

METHODS

Patient selection

Patients in this study were recruited from among 130 patients already undergoing treatment at our dialysis center. The main inclusion criterion was the availability of an optimal chest acoustic window to allow a state of the art echocardiogram to be made. Other inclusion criteria were to have been enrolled in a regular renal replacement treatment program for at least six months and a willingness to participate in the study. The exclusion criterion was an existence of concurrent illness, such as chronic inflammatory diseases and cancer, besides well-known causes of LVH except for arterial hypertension (such as diabetes, coronary arterial disease, significant valvular regurgitation, congestive heart failure, and severe uremic anemia) [11]. Patients were also excluded if they had a frequent recurrence of intradialytic hypotension, defined according to criteria reported elsewhere [12].

After these inclusion and exclusion criteria were met, the records of each patient were retrieved, and only subjects not having undergone major changes (±5%) in their prescribed ideal "dry" body weight or modifications in their antihypertensive regimen over the previous three months were chosen. Thus, the final study group consisted of 55 patients, 24 women and 31 men, whose ages ranged from 24 to 74 years and who had already been on renal replacement therapy for at least six months. Renal diseases causing end-stage renal failure were: glomerulonephritis in 20 patients, adult polycystic kidney disease in 9, hypertensive nephrosclerosis in 9, interstitial nephropathies in 10, other causes or unknown etiologies in 7 patients.

All subjects were on dialysis three times per week with standard bicarbonate dialysis or high-flux hemodiafiltration. Treatment lasted from 4 to 4.5 hours and the dialyzer surface area ranged from 1.3 to 1.8 m^2; both of these were prescribed on an individual basis in an attempt to obtain a $Kt/V_{urea} \geq 1.2$. The intradialytic body weight decrease was individually modeled by controlled ultrafiltration with the aid of computer-assisted dialysis machines. The solute concentrations in the dialysis bath were as follows: sodium from 139 to 141, potassium from 2.5 to 3.5, calcium from 2.5 to 3, and bicarbonate from 33 to 35 mEq/L.

The ideal "dry" body weight was established according to clinical and instrumental diagnostic procedures, as previously reported [13]. The subjects' diets consisted of 1.1 to 1.2 g of protein content per day, with unrestricted cooking salt but with no canned or salty-tasting foods. If, however, the patients experienced excessive thirst or disproportionate interdialytic body weight gain (IWG), a salt-restricted diet with no more than 4 g of salt per day was prescribed until the symptoms subsided.

Most patients were treated with recombinant human erythropoietin (rHuEPO) aimed at keeping their predialysis hemoglobin (Hb) level at approximately 10 g/dL. They were also administered oral or intravenous calcitriol and calcium-containing salt phosphate binders. Some of them had already been on treatment with one or more antihypertensive drugs for varying periods of time in order to control arterial hypertension. The drugs included the angiotensin-converting enzyme (ACE) inhibitor lisinopril at dosages ranging from 2.5 mg on alternate days to 20 mg a day, the calcium channel blocker nifedipine 30 mg a day, and the β blocker atenolol up to 50 mg a day. Therapy was given on a daily basis regardless of the dialytic schedule of each individual patient. Sera were routinely tested at least monthly after a long interdialysis interval to measure predialysis Hb, urea, and circulating parathyroid hormone (iPTH).

Procedures and study protocol

All of the clinical blood pressure (BP) measurements obtained by mercury sphygmomanometer, as well as the body weight measurements recorded by the nurses before and after the 12 hemodialysis (HD) sessions done the month preceding the study, were retrieved and stored for subsequent statistical analyses. The number and dosages of antihypertensive drugs used over the previous three-month period were also recorded.

Continuous ambulatory BP monitoring took place in the morning before a midweek interdialysis day. Before the fistula needle was inserted, each patient was equipped with a portable BP monitor (Spacelab 90207) in order to provide BP measurements over the following 24 hours. Further BP monitoring beyond this limit was ruled out by the unwillingness of most of the subjects to wear the monitor for a long period of time. Monitored BP records were taken every 30 minutes during conventional waking hours (until 8 p.m.) and every 60 minutes during evening and sleeping hours (from 8 p.m. to 8 a.m.). Just before the following HD, which took place 48 hours later, the patients rested supine in their beds, and their BP was again monitored every 5 minutes for 15 minutes. These measurements were averaged and were considered representative of the monitored BP levels actually present at that time.

Echocardiography was arranged and performed in all subjects on a midweek interdialysis day, usually within a week before or after ambulatory BP monitoring. The measurements included the end systolic (ESD) and diastolic (EDD) diameters of the left ventricle, the interventricular septum (IVS) thickness, the thickness of the posterior left ventricular wall (PW), and the diameter of the left atrium (LA). The criteria for adequacy of collection, reading, and reproducibility of our echocardiographic measurements have been reported elsewhere [11].

Definitions, calculations, and statistics

The upper limits for normal sphygmomanometric systolic/diastolic and mean BPs (mBPs) were 140/90 and 106.6 mm Hg, as already set forth by the JNC VI [14]. All subjects having BPs above these limits were considered hypertensive. Likewise, the thresholds for normality of the ambulatory-monitored BP were 133/81 and 98.3 mm Hg, as already established by Staessen et al [15]. Classification of patients as "dippers" and "nondippers" was made according to the criteria issued by the same group [16].

Blood pressure responsiveness to HD was defined as a greater than 5% decrease of the mBP according to the criterion proposed by Sullivan et al [17].

The presence or absence of LVH was defined on the basis of a calculated [18], indexed left ventricular mass (LVM) $\geq$120 g/m^2/body surface area (BSA) [11]. The fractional shortening (% FS) of the LV was calculated as EDD-ESD/EDD $\times$ 100.

Data are presented as mean $\pm$ SD and ranges. The Student's *t*-test was used for comparison between two groups. Comparisons among groups at any given time were made by analysis of variance (ANOVA). Significant differences in measurements within a single group or between groups over time were assessed by ANOVA for repeated measures. When the *F* test was significant, Sheffè's post hoc test for multiple comparisons was calculated. The significance of associations between two variables were assessed by calculating the Pearson's rank correlation coefficient (Rp), while linear regression was calculated by the least-squares method. Significant differences between regression lines were assessed by the analysis of covariance (ANCOVA). Frequencies among groups were compared by the χ^2 test, while Fisher's exact test was used when appropriate. Concordance between categorical variables was assessed by calculating the "k" Cohen's coefficient of concordance.

RESULTS

The average BP measurements collected by nurses before and after the 12 hemodialyses performed the month preceding the study were predialysis systolic, 142 $\pm$ 15 (range 102 to 165) mm Hg, and diastolic, 80 $\pm$ 9 (57 to 100) mm Hg, while postdialysis BPs were 135 $\pm$ 16 (101 to 180) and 77 $\pm$ 9 (58 to 100) mm Hg. Overall, the BP decreases induced by HD were significant for both systolic (t = 4.55, $P < 0.0001$) and diastolic (t = 3.38, $P < 0.0013$) values. The decreases in body weight from 64.3 $\pm$ 12.3 kg before to 61.8 $\pm$ 12 kg after dialyses were also significant (t = 23.6, $P < 0.0001$).

Echocardiography performed during the week before or after test-HD revealed that 46 out of 55 patients in the study had LVH.

Pretest-HD monitored BPs were systolic 144 $\pm$ 19 (95 to 182) mm Hg, which were not significantly different from the monthly averaged sphygmomanometrically collected BPs (t = 1.41) and diastolic 85 $\pm$ 12 (64 to 124) mm Hg, which were slightly but significantly higher (+5.3 mm Hg; CI, 2.6 to 7.9; t = 4.01, $P < 0.0002$). There were close correlations for both systolic (Rp = 0.74, $P < 0.0001$) and diastolic BPs (Rp = 0.58, $P < 0.0001$) between the two sets of data as well as between each of these BP measurements and LVM. These relationships were Rp = 0.54, $P < 0.0001$ (for monitored systolic); Rp = 0.51, $P < 0.0001$ (for manual systolic); Rp = 0.46, $P = 0.0004$ (for monitored diastolic); and Rp = 0.38, $P = 0.004$ (for manual diastolic).

Classification of the patients as hypertensive or normotensive on the basis of predialysis systolic BPs revealed that according to the ambulatory BP monitoring criteria (cut-off systolic BP = 133 mm Hg), 45 out of 55 patients (82%) were hypertensive, while according to the JNC VI criterion (cut-off = 140 mm Hg) 36 out of 55 (65%) were hypertensive (Table 1). Classification of patients using these two criteria was not significantly discordant (k = 0.41, $P < 0.001$), although there was disagreement as far as 13 patients were concerned. Eleven out of 13 of these patients were normotensive according to the nurses but were hypertensive according to the BP monitor (Table 1). Their corresponding BP values were 129 $\pm$ 8 (108 to 139) and 142 $\pm$ 8 (133 to 157) mm Hg, which differed significantly (t = 5.18, P = 0.0004).

When the same analyses were made for diastolic BPs, it appeared that there were 33 out of 55 (60%) patients who were hypertensive according to the BP monitor and only 7 out of 55 (13%) who were hypertensive according to the manual BP measurements (Table 1). Classification of patients by these two criteria was not concordant (k = 0.11; P = NS). The main disagreement between the two classifications consisted of 27 patients who were classified as normotensive by the nurses and who proved to be hypertensive by the BP monitor. Diastolic BPs for these patients according to the two methods were 82 $\pm$ 5 (70 to 89) and 91 $\pm$ 9 (81 to 124) mm Hg, respectively, which were significantly different (t = 6.29, $P < 0.0001$).

When the same analyses were made for mean BP values, there were 14 (25%) concordant normotensive

Table 1. Patient classification

Portable monitor	Sphygmomanometry	Predialysis			Postdialysis		
		Systolic BP	Diastolic BP	Mean BP	Systolic BP	Diastolic BP	Mean BP
Normotensive	Normotensive	8 (14%)	21 (38%)	14 (25%)	29 (53%)	36 (65%)	37 (68%)
Normotensive	Hypertensive	2 (4%)	1 (2%)	0	12 (22%)	0	2 (4%)
Hypertensive	Normotensive	11 (20%)	27 (49%)	23 (42%)	3 (5%)	14 (26%)	8 (14%)
Hypertensive	Hypertensive	34 (62%)	6 (11%)	18 (33%)	11 (20%)	5 (9%)	8 (14%)

Classification of 55 dialyzed uremics as normotensives or hypertensives was according to the pre- and postdialysis blood pressure (BP) levels measured with two different methods of BP measurement entailing different cut-off limits for discriminating normal from supranormal BP levels.

patients, 18 (33%) concordant hypertensive patients, and 23 patients (42%) who were considered normotensive by the nurses and hypertensive by the BP monitor (Table 1). The corresponding monitored and manual BP levels for these 23 patients were 108 ± 7 (99 to 124) and 99 ± 5 (88 to 105) mm Hg, which differed significantly ($t = 5.8, P < 0.0001$). Furthermore, the LVM of these patients was 174 ± 43 (112 to 263) g/m^2 BSA, which was significantly higher than concordant normotensives [132 ± 27 (84 to 191) g/m^2 BSA, $P < 0.01$], but similar to those of concordant hypertensives [189 ± 39 (128 to 267) g/m^2 BSA, P = NS].

Post-test-HD monitored diastolic BPs were 76 ± 12 (57 to 110) mm Hg, which were not significantly different from the monthly averaged sphygmomanometrically collected BPs, and systolic BPs 126 ± 19 (96 to 179) mm Hg, which were significantly lower [−9.4 (CI, 4.95 to 13.85) mm Hg, $t = 4.24$, $P < 0.0001$)].There were close correlations for both diastolic (Rp = 0.613, $P < 0.0001$) and systolic BPs (Rp = 0.567, $P < 0.0001$) between the two sets of data. Furthermore, there were significant correlations between these BP measurements and the LVM.

Analyzing the classification of patients, which was made on the basis of the criteria underlying the two methods of BP measurement, revealed that there were no statistical discordances between them (Table 1).

After filtering out the patients who were discordantly classified according to the two methods of BP measurement, all of the correlations previously found between the different sets of BP measurements strengthened greatly. This fact was impressive as far as systolic BP values before dialysis were concerned in that the BP measured by one method closely approached the identity to the BP measured by the other ($N = 42$, Rp = 0.84, graph not shown).

Test HD procedures were carried out in all cases with no technical inconvenience and HD proved to be uneventful in all subjects.

Preliminary statistical analyses revealed that there were correlations between each set of systolic, diastolic, and mean monitored BP values recorded at any given time and the LVM. The ANCOVA analysis, however, demonstrated that the strongest correlation was the one between LVM and mean BP recorded at the 24th hour (Fig. 1 shows this relationship).

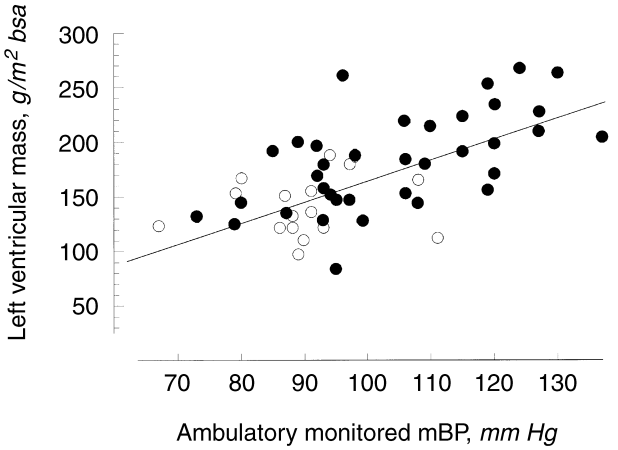

Fig. 1. Correlation between levels of mean blood pressure measured 24 hours after the end of hemodialysis (HD) with a portable monitor in 55 uremic patients and the corresponding values for the indexed left ventricular mass (LVM) in the same subjects. The closed circles (●) indicate patients on antihypertensive therapy for at least six months ($r = 0.63$; $P < 0.0001$).

Scrutiny of the monitored BP records of each individual patient revealed that the patients' BP values behaved differently over time, thus allowing us to identify four distinct groups of patients (Fig. 2). One group (group A, $N = 14$) had persistently normal monitored BP, and another one (group D, $N = 13$) had persistently supranormal BP levels. There were also two other groups whose BP levels were high before HD, normalized after HD, then increased again, either soon after HD (group C, $N = 9$) or later on following HD (group B, $N = 19$).

Statistical analysis made by ANOVA for repeated measures confirmed that there were indeed differences among these four groups over the entire time frame of observation ($F = 83.46$, $P < 0.0001$). This means that differences were detectable between two or more than two groups at any given time ($F = 37.29$, $P < 0.0001$).

Before HD, there were differences between group A and group B ($t = 9.36$, $P = 0.0001$) and between group B and group D ($t = 4.4$, $P = 0.0001$).

Overall, the BP behavior in group A changed signifi-

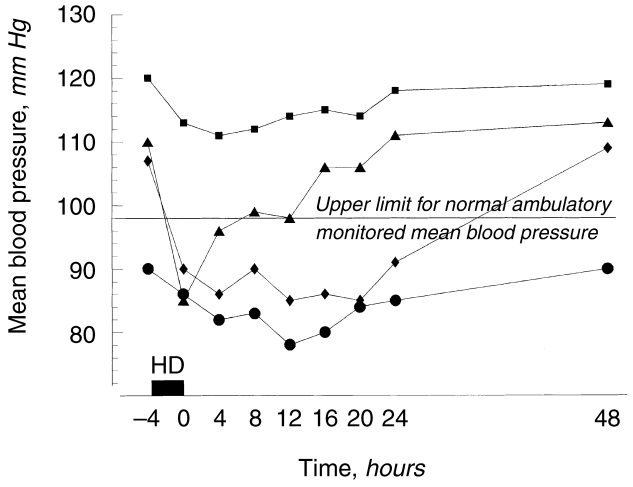

Fig. 2. Average levels for the mean BP measured by a portable monitor for four groups [group A (●), $N = 14$; group B (◆), $N = 19$; group C (▲), $N = 9$; group D (■), $N = 13$] of dialyzed uremics over a period that included a single dialysis treatment (Uf-HD). BP levels were different over time in these four groups ($F = 83.46$; $P < 0.0001$ by ANOVA), since differences were detectable between two or more than two groups at any given time ($F = 37.29$, $P < 0.0001$).

cantly ($F = 3.7$, $P = 0.0007$). It tended to decrease slightly but continuously from before HD onward, and by the 12th hour had become significantly lower than before HD ($P < 0.01$). From then on, however, it started to gradually increase. By 48 hours, it no longer differed in comparison with those recorded before HD.

In both groups B and C, BP during HD decreased to the same extent ($t = 7.62$, $P < 0.001$, and $t = 5.46$, $P < 0.001$, respectively). From that point onward, however, the BP behavior between the two groups diverged. Although the BP level in group B remained nearly unvaried until 24 hours, it was still high when remeasured before the next HD. In group C, the BP started rising as of the fourth hour ($P = 0.01$) after the end of HD. BP levels in group D tended to decrease from the before to after HD measurements. This decrease, however, was not significant and even completely disappeared, although gradually, afterward.

Since analysis of the individual BP behavior allowed us to classify four distinct groups of patients, we were encouraged to further analyze the data and to look for other differences, if any, that would distinguish these groups. Some of the data taken into consideration are listed in Table 2.

There were no differences among the four groups as far as distribution of etiologies of underlying renal diseases, gender ratios, or age were concerned. The most relevant difference, besides BP levels, that distinguished the four groups was the LVM (Table 2). LVMs, in fact, were lower in groups A and B than in groups C and D (P at least <0.002), while the differences between groups A and B and between groups C and D were not remarkable. These differences in LVMs were mostly accounted for by differences in the PW and in the IVS, and by slight but insignificant differences in the EDD. No other relevant differences in the cardiac measurements were found, although the LA tended to be larger in groups C and D, and the % FS of the LV tended to be lower in group C. Other relevant differences were those regarding dialytic age, which was significantly higher in group A patients, who also had a tendency for higher Kt/V_{urea} values (Table 2).

No other statistical differences were detectable among the groups as far as serum PTH and Hb levels were concerned or regarding the weekly average dose of rHuEPO administered to each group.

With regards to the use of antihypertensive drugs, the number of subjects on antihypertensive therapy differed among the four groups (Table 2). The main difference (Fisher's $P = 0.0019$), however, was found between group A, where 43% of the patients were taking drugs, and group D, all of whom were already on antihypertensive treatment. No other differences were found concerning time elapsed since the beginning of therapy, number of drugs given to each treated patient, number of patients taking ACE inhibitors, or as far as ACE inhibitor dosages were concerned (Table 2).

DISCUSSION

One of the reasons for the high prevalence of arterial hypertension in dialysis patients might be in the way physicians treat arterial hypertension once it has been diagnosed. Classifying one as a hypertensive subject is a difficult task, since the BP threshold that antihypertensive treatment should be started at is quite discretional unless definite, attendant end-organ damage is documented [19]. The issue is rendered even more complicated by the intrinsic variability of BP over time [20], the discrepancies between the methods of BP measurements [20], as well as by common errors in correctly measuring the true average BP levels [21].

Admittedly, all of these shortcomings inherent to BP management in the general nonuremic population also apply to the treatment of arterial hypertension in dialysis patients. The task is even more difficult in these patients because of the wide BP fluctuations that typically occur during and between dialyses as a result of the diffusive dialytic procedure and of the manipulations and variations of the extracellular fluid volume (ECFV) [22]. In fact, there are great uncertainties regarding the best method for measuring BP (manual vs. monitored), regarding the BP levels that should be considered pathological, and regarding the best time (before dialysis, during dialysis, after dialysis, interdialytic off-day dialysis) for collecting reliable BP readings [8].

Table 2. Comparisons of demographic, clinical and echocardiographic data for four groups of patients with different BP behaviors during and between dialysis treatments

Variable	Group A	Group B	Group C	Group D	Test	*P* value
N	14	19	9	13		
Dialytic age *months*	109 ± 54	45 ± 35	48 ± 44	72 ± 46	ANOVA	0.0011
Monthly averaged pre-HD mBP *mm Hg*	91 ± 10	101 ± 7	106 ± 6	106 ± 7	ANOVA	0.0001
Monthly averaged post-HD mBP *mm Hg*	89 ± 10	96 ± 8	98 ± 11	104 ± 7	ANOVA	0.0016
Dippers/nondippers	6/8	12/7	2/7	7/6	χ^2	NS
On antihypertensive therapy *yes/no*	6/8	13/6	7/2	13/0	χ^2	0.012
On ACE inhibitors *yes/no*	5/1	12/1	7/0	13/0	χ^2	NS
One drug/two drugs/three drugs	5/0/1	5/5/3	4/1/2	7/5/1	χ^2	NS
%IWG *kg*	4.0 ± 1.0	4.4 ± 1.3	4.8 ± 1.8	3.6 ± 1.1	ANOVA	NS
IVS *mm*	11.7 ± 2.4	12.5 ± 1.7	12.9 ± 1.4	14.1 ± 2.5	ANOVA	0.036
PW *mm*	10.2 ± 1.4	10.7 ± 1.9	11.8 ± 1.2	12.2 ± 1.9	ANOVA	0.013
EDD index *mm/m² BSA*	28.7 ± 4.2	29.8 ± 2.6	32.3 ± 3.8	31.2 ± 5.3	ANOVA	NS
LVMi *g/m² BSA*	132 ± 27	156 ± 26	201 ± 51	200 ± 36	ANOVA	0.0001
LA index *mm/m² BSA*	21.6 ± 3.9	21.6 ± 3.3	24.2 ± 8.2	23.1 ± 4.1	ANOVA	NS
% FS	42 ± 6	39 ± 7	35 ± 8	40 ± 6	ANOVA	NS
Hb *g/dL*	10.5 ± 0.7	9.9 ± 1.3	9.8 ± 1.1	9.7 ± 1.3	ANOVA	NS
iPTH *pg/ml*	279 ± 231	205 ± 157	166 ± 192	172 ± 185	ANOVA	NS
Kt/V	1.33 ± 0.21	1.18 ± 0.17	1.19 ± 0.17	1.20 ± 0.11	ANOVA	NS
rHuEpo dose *IU/kg/week*	118 ± 84	127 ± 89	96 ± 74	135 ± 64	ANOVA	NS

Abbreviations are: HD, hemodialysis; mBP, mean blood pressure; ACE inhibitors, angiotensin converting enzyme inhibitors; IWG, interdialytic weight gain; IVS, interventricular septum; PW, left ventricular posterior wall; EDD, left ventricular end diastolic diameter; LA, left atrium; LVMi, left ventricular mass index; FS, left ventricular fractional shortening; Hb, hemoglobin concentration; iPTH, intact parathyroid hormone; rHuEpo, recombinant human erythropoietin. Data are given as mean ± SD, when appropriate.

Left ventricular hypertrophy is said to be not only the result of long-lasting arterial hypertension [4], but also strongly associated to present or oncoming coronary, peripheral, and cerebrovascular diseases [2, 23]. Therefore, measuring the LV would be an aggregate measurement of the end-organ effects of raised BP, which would be a less controversial marker of long-lasting arterial hypertension than are elusive or questionable spot BP measurements [19, 24]. This was the reason that we used echocardiographic measurements of the LV together with a series of clinical and monitored BP data to verify the soundness of our own criteria for identifying and treating arterial hypertension. Therefore, we only selected patients without well-known LVH-inducing causes, except for arterial hypertension. This accounts for the exclusion of patients with diabetes that might have an independent pro-growth effect on the LVM [25]. One relevant finding of our study is the strong, direct association between BP and LVM. Such a finding is not new, as it has already been reported in studies of dialysis patients [26, 27]. What is surprising is the unprecedented strength of the association we found between these two parameters. Most of our patients were being treated with ACE inhibitors, which might have an LVM-lowering effect, regardless of their hypotensive effects [12]. Thus, it is possible that the strong BP-LVM relationship we found might have been even stronger had the patients not been undergoing treatment with these drugs.

In our study, absolute values of manual and clinical BP levels were closely correlated to each other when discordant measurements were discarded. However, there were too many discrepancies between the two methods of measurement in that manual measurements were generally lower than those measured by the monitor. LVMs of patients who were discordantly classified by the two methods were more closely correlated to monitored rather than manual BPs. Thus, on the basis of these findings, we suspect that a considerable number of patients who were actually hypertensive might have been erroneously classified as normotensive by the nurses. Such errors in measuring clinical BP levels in dialyzed uremics are not irrelevant, as one might attribute a false normotensive classification to subjects who are actually hypertensive, thus possibly causing the link between arterial hypertension and LVH to be missed. This may be relevant if one thinks of the early studies appearing in the late 1980s, which failed to uncover any relationship between clinically measured BP and LVH [28, 29].

Close scrutiny of the individual BP behavior during dialysis and over the period between dialyses allowed us to roughly distinguish four groups of patients. The average dimensions of the internal diastolic left ventricular diameter and of the LA did not differ significantly among groups. In previous studies, left atrial dimensions of dialyzed uremics were strictly correlated to the intravascular volume loads [30, 31], as well as to the total blood volume and to the plasma concentrations of the atrial natriuretic peptide [30]. Thus, it seems unlikely that our patients had grossly divergent ECFV levels. In spite of this, in the face of similar ECFV unloading with dialysis, the BP of some patients (namely, those in groups A and D) remained nearly unaffected, while the BP of others (groups B and C) was greatly lowered. Moreover, inspection of BP behavior in group A clearly indicates

that HD treatment induced a prolonged BP decrease that lasted far beyond the end of volume unloading. Thus, it appears that the diffusive process inherent to the dialytic treatment might have had a BP-lowering effect regardless of intravascular volume unloading. It is impossible to tell to what extent this volume-independent hypotensive effect(s) might also have contributed to the BP decrease in groups B and C.

In this study, BP increased considerably in nearly one half of the patients between dialysis treatments, in spite of a body weight gain that was quite similar to patients whose BP values rarely varied. Differences in individual BP sensitivity to intravascular volume re-expansion might account for this observation [32]. Subjects whose BP levels had increased were the same ones whose BP values completely normalized following the dialytic treatment. Thus, these findings strongly support the study by Cheigh et al in which BP monitoring unveiled uncontrolled arterial hypertension between dialyses in patients already deemed as having "volume-responsive arterial hypertension" [22].

Regardless of the mechanism(s) causing BP to increase in some patients during the interdialysis interval, what is remarkable is that this unfavorable BP behavior was associated with LVH. Furthermore, it is also noteworthy that the degree of LV overgrowth in these subjects was roughly inversely related to the amount of time they had remained normotensive. However, hypertension-dependent LVH requires some time to develop [2]. Therefore, it is likely that the LVH detected in our patients was a consequence of customary rather than occasional BP behavior.

In a previous study of dialysis patients, inadequate strength of antihypertensive therapy was thought to be the reason why neither raised BP levels nor LVH improved satisfactorily under prolonged antihypertensive therapy [13]. In this study, only a few patients whose BP was high and whose LVM was heavy were left untreated (Fig. 1). On the other hand, it must also be said that the treated patients were on antihypertensive therapy of equal strength in spite of different degrees of severity of both arterial hypertension and LVH. The pitfalls discovered by our analysis and the ensuing clinical misjudgments that can be engendered might collectively account for our underestimating the severity of the hypertensive disease.

One limit to this study is that it is, indeed, only a single-center study. Should our data be representative of the difficulties and the pitfalls inherent to the approach of arterial hypertension in dialysis centers worldwide, a reappraisal of the current approach to this clinical problem would be warranted.

First, there were mistakes in the way our nurses measured BP levels. These errors were more frequent before, rather than after dialysis when the environment is less busy. Therefore, understaffing and huge pressures on personnel and technicians should be minimized. Careful training of the nurses—including occasional confirmation of their ability to collect sphygmomanometric BP correctly—should also be required [21]. The errors more frequently affected diastolic than systolic BP. Thus, systolic rather than diastolic BP should be used as a reliable reference BP value, since the former is better at detecting raised BP levels [21]. Furthermore, since postdialysis BP readings might be deeply affected by the hypotensive effects induced by the diffusive process, it is probably wise to rely on predialysis rather than postdialysis BP data. The deceptive nature of these data, in fact, might engender reluctance in prescribing or strengthening hypertensive therapy. Furthermore, establishing the dry body weight on the basis of postdialysis BP in an attempt to correct a fictitious ECFV contraction might lead to the development of chronic hypervolemia and further worsening of hypertension. Each subject whose predialysis systolic BP is high should probably be considered hypertensive, no matter how much his or her BP decreases from before-to-after dialysis. Except for the few hours during and after dialysis treatment, in fact, the BP of these patients remains considerably elevated, while their LVH might worsen relentlessly. From a practical point of view, therefore, once a frank volume overload has been ruled out, it is probably wise to treat these patients with drugs or to reinforce their antihypertensive treatment disregarding the few hours of apparently normal BP levels they experience.

Finally, our study has further convinced us of the usefulness of echocardiography in correctly diagnosing arterial hypertension. What we have learned is that every effort should be made to rule out underlying arterial hypertension in uremic subjects with seemingly normal clinical BP and raised LVM. Moreover, periodic echocardiography (once or twice a year) [12, 13] would also provide a useful tool for tailoring and monitoring effective antihypertensive therapy and, in dubious cases, could also provide an objective estimate of the intravascular volume load [30].

The last JNC indicates 120/80 mm Hg as the optimal BP [14]. In this study, only 9 out of 55 patients had almost normal or normalized LVMs (Fig. 1). The predialysis systolic BP of these patients was 131 ± 19 mm Hg, ranging from 102 to 148 mm Hg. Thus, a systolic BP lower than 148 mm Hg should be the target of antihypertensive therapy, which is aimed at reversing LVH.

Besides BP control, proper dialysis adequacy might also be relevant when dealing with LVH of hypertensive patients on dialysis. It should be noted that all patients who had normal LVM belonged to group A. This group had higher dialytic ages, as well as a tendency toward higher Kt/V_{urea} values. There may be a link between high Kt/V_{urea} values, BP control, LVH, and survival [33].

Therefore, adequate dialysis dose delivery and strict BP control could improve the otherwise poor cardiovascular prognosis and the overall survival of uremic patients. Actuarial survival time of patients with LVH in our center is approximately 58% after five years (unpublished data). Most likely this percentage will increase in the near future if we are able to deal with the prevalence and severity of arterial hypertension more effectively.

On the basis of the JNC VI criteria [14], approximately 65% of the patients in the present study had arterial hypertension or were being treated with antihypertensive drugs. This figure compares well with recent reports on larger series of dialyzed uremic patients both in Europe and in the United States [8, 34, 35]. However, it stands in poor contrast with the studies by French authors [33], who reported excellent BP data, although combined with persistent LVH, for uremic patients undergoing long-lasting dialysis treatment (abstract; Luik et al, *J Am Soc Nephrol* 5:521, 1994).

Requests for dialysis treatment are quickly increasing worldwide, thus imposing short-lasting, poorly flexible dialysis schedules in order to comply with these demands. Furthermore, long-hour dialysis schedules would hardly be acceptable by most of our patients. Our study results suggest that the potential improvement in our current approach to arterial hypertension might still go far enough without having to resort to difficult to adopt dialysis procedures.

ACKNOWLEDGMENTS

This study was supported by a research grant from the Associazione Nefrologica Genovese, Genova, Italy.

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