Peripheral artery disease and blood pressure profile abnormalities in hemodialysis patients

Francesca Viazzi, Giovanna Leoncini, Elena Ratto, Giulia Storace, Annalisa Gonnella, Debora Garneri , Barbara Bonino, Francesca Cappadona, Emanuele L Parodi, Daniela Verzola, Giacomo Garibotto, Roberto Pontremoli.

The work was conducted in the Department of Internal Medicine, University of Genova and IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Genoa, Italy

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Corresponding Author:

Francesca Viazzi

Department of Internal Medicine, University of Genova and IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Genoa, Italy

Viale Benedetto XV, 16132 Genova; telephone +39 0103538496; fax +39 0103538932

francesca.viazzi@unige.it

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Abstract

Background Patients undergoing chronic hemodialysis (HD) are at increased risk for peripheral artery disease (PAD). Both ankle-brachial index (ABI) and ambulatory blood pressure monitoring (ABPM) in the interdialytic period showed to be strong predictors of all-cause mortality.

Methods This cross- sectional study investigates the relationship between ABPM profile and ABI in 81 HD patients. **A**BPM was measured throughout a 44-h midweek interdialytic period. Pre dialysis ABI was evaluated with a BOSO ABI device. An ABI value <0.9 or >=1.3 was defined as abnormal.

Results. In the whole study group (72% males, mean age 67±14 years), there was an increase in BP ($p<0.05$) and in systolic BP night/day ratio (n/dSR , $p=0.01$) during the interdialytic period.

Patients with abnormal ABI (n=29) more frequently showed a positive history for cerebrovascular accident, and PAD and had higher ProBNP values compared to those with normal ABI (n=52). No difference was detected among ABPM-derived components except for the n/dSR ($p=0.02$).

Patients with abnormal ABI showed a significant increase of n/dSR ($p=0.02$) and ambulatory arterial stiffness index (AASI) ($p=0.006$) in the second day respect to the first.

Patients with n/dSR >1 during day 2 (n=34) where older, showed significantly higher ProBNP and AASI and were more likely to reveal abnormal ABI as compared to those with a lower n/dSR ($p=0.006$)

Conclusions: Abnormal ABI in HD patients is associated to changes in interdialytic ABPM pattern, namely higher n/dSR in the second day. These data may provide pathophysiological mechanisms underlying for the worse outcome observed in HD patients.

Key words: Ambulatory blood pressure monitoring, hemodialysis, hypertension, peripheral artery disease, stiffness

Introduction

Peripheral artery disease (PAD) is highly prevalent in patients with end stage renal disease (ESRD) undergoing chronic hemodialysis (HD) and is a strong predictor for subsequent cardiovascular and all-cause mortality (1-2). Ankle-brachial index (ABI) is a simple, noninvasive, and reliable test for PAD screening. Both low (<0.9), and high (>=1.3) values have been strongly related to an unfavorable outcome in HD patients (3-4) as compared to normal values.

Hypertension is common among patients with chronic kidney disease and often remains poorly controlled in HD patients (5). Furthermore, there is currently some debate about which method should be preferred to establish the diagnosis of hypertension in patients undergoing HD. BP recorded both before and after dialysis, even when measured by standardized techniques, agrees poorly with ambulatory BP values taken during the interdialytic period (6-7). Interestingly, clinic BP obtained outside the dialysis unit, whether by interdialytic automatic devices or self-measured at home, well correlates with left ventricular hypertrophy (8). More recently, home and ambulatory BP recordings were found to carry greater prognostic power when compared to clinic BP recorded just before and after dialysis (9). As a matter of fact, ambulatory blood pressure monitoring (ABPM) provides measures of night-time as well as diurnal pressure load and their relationship, which have been shown to be accurate predictors of risk. Furthermore, several reports suggest that the prognostic information is nearly completely contained in the systolic component of BP, rather than the diastolic one. Accordingly, the night/day systolic ratio (n/dSR) showed to be associated with all-cause and cardiovascular mortality in hemodialysis nondiabetic patients without pre-existing cardiovascular events (10) over and beyond the BP level. As arterial stiffness and interdialytic weight gain are both known to influence BP behavior, HD patients have been demonstrated to show marked abnormalities in interdialytic ABPM patterns, namely a blunted circadian amplitude and a steady rise in blood pressure between dialysis treatments (11). Nevertheless, whether atherosclerotic damage contributes to modulate this circadian behavior is not at the present known.

Looking at the relationship between atherosclerotic disease and BP behavior in ESRD patients undergoing HD might help clarify the pathophysiological processes underlying the striking increase of cardiovascular morbidity and mortality recorded in these patients.

Methods

Participants

After obtaining written informed consent , patients 18 years or older who had ESRD and had been treated with chronic HD three times a week for at least 3 months at our center were subjects for this study approved by the Ethical Committee of our Departmen.t. Patients were excluded if body mass index of ≥40 kg/m2, history of missing one or more hemodialysis treatments in the previous month, known drug abuse, severe chronic obstructive pulmonary disease, stroke or myocardial infarction within the previous 6 months.

Routine laboratory parameters were collected pre-dialysis on the study day, except for NT-ProBNP that was calculated as the mean of two separate pre-dialysis samples taken within two weeks before and after the study day. The presence of lower limbs atherosclerotic damage (from asymptomatic US detected vascular abnormalities to clinically relevant atherosclerotic disease included revascularization) was defined PAD.

Ambulatory BP monitoring

Ambulatory BP monitoring was performed after the midweek hemodialysis session for 44 h. Ambulatory BPs were recorded every 20 min during the day (6 AM to 10 PM) and every 30 min during the night (10 PM to 6 AM) using a TM-2430 (A&D Instruments LTD, Oxford, UK) in the nonaccess arm. Recordings began immediately after hemodialysis and were terminated immediately before the subsequent dialysis session. Accuracy of ambulatory BP recordings was confirmed against auscultated BP at baseline. Data were analyzed using Cardiovascular Management software, version B.01.00 (Intermed SRL). A diagnosis of hypertension was made if the 44-h interdialytic ambulatory BP monitoring was ≥135 mmHg systolic or ≥85 mmHg diastolic or in presence of antihypertensive treatment. Uncontrolled hypertension was defined when interdialytic ambulatory BP monitoring was ≥135 mmHg systolic or ≥85 mmHg diastolic in presence of antihypertensive treatment (12). Ambulatory BP records with a number of readings adequate for investigating the night and day behavior in both interdialytic days (at least 37 readings during day-time and 13 readings during night-time) was obtained in 77 hemodialysis patients. Nocturnal dipping was defined as a 10% reduction in the average SBP at night as compared with the average awake values. Ambulatory arterial stiffness index ($AASI_{44}$, $AASI_{I22}$, $AASI_{II22}$) was calculated as 1 minus the regression slope of DBP plotted against SBP obtained from individual 44, first 22, and second 22 -h BP monitoring, respectively (13). The slope was not forced through the origin. We used the standard deviation (SD) as index of short-term reading-to-reading blood pressure variability (BPV). We

calculated the SD of the mean of all individual readings over the first and the second day and night periods separately. The n/dSR was calculated for each interdialytic day as the ratio of the average value of SBP during the night and the corresponding average value of SBP during the day. A n/dSR value>1 indicates a non-dipping pattern characterized by an increase of BP levels during nigh-time respect to day-time (i.e., reverse dipping or rising pattern).

ABI Measurement

Automated ABI measurements was performed using a professional oscillometric BP monitor (BOSO ABI System 100) allowing simultaneous arm-leg BP measurements. Briefly, measurements were done pre dialysis, on non-access extremities with the patient at rest in the supine position for 5 -10 minutes. The measurements were performed by the same examiner (AG) in all situations. ABI was classified as abnormal when it was < 0.9 or >= 1.3.

Statistical analysis

Variables are expressed as arithmetic mean±standard deviation. Skewed variables were log-transformed before statistical analysis was carried out. Categorical variables are expressed as proportions. Comparison of proportion among groups was performed by using the x2 test. Comparisons among groups were made by analysis of variance.
Logistic regression analysis was used to describe the relationship between volume status (NT-proBNP), arterial stiffness (AASI) and vascular damage (ABI) and the presence of n/dSR>1 during second day. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated by exponentiation of logistic regression coefficients. Statistical analyses were performed using Statview for Windows (SAS Institute Inc., version 5.0.1, Cary, North Carolina, USA). P value less than 0.05 was considered statistically significant.

Results

Table 1 presents demographic, clinical and routine pre-dialysis laboratory parameters of study subjects. A total of 81 patients (58 men and 23 women) with a mean age of 67.4 ± 14.1 years, receiving hemodialysis for a median of 33 months (IQ range: 63 months) were included. About 24% of participants were diabetics, 76% were hypertensives (40% uncontrolled), 76% had left ventricular hypertrophy (by ECG or Echocardiography), 66% showed peripheral vascular disease, 13% had history of cerebrovascular disease. As for antihypertensive treatment, β-blockers (53%), loop diuretics (39%) and calcium antagonists (33%) were the most commonly prescribed drug classes. Ambulatory BP measurements during the first and second interdialytic days are presented in Table 2 (unadjusted repeated measures ANOVA). There was a significant increase in BP during the interdialytic period ($p<0.05$) and this rise was consistent for both day-time and night-time periods (data not shown). With regard to the night and day behavior, the n/dSR increased in the second as compared to the first day ($p<0.01$) and, accordingly, the percentage of dipping status during the second day was reduced respect to the first interdialytic day (27 vs 37%, $p=0.01$).

ABI resulted abnormal in 36% of the study patients and was >= 1.3 in 4 patients out of 29. Patients with abnormal ABI more frequently showed a positive history of ischemic cerebrovascular accident and PAD. Moreover, they had higher fasting plasma glucose, HbA1c and ProBNP values and lower plasmatic creatinine and HDL- cholesterol levels as compared to those with normal ABI (n=52) (Table 1). No difference has been detected among 44- and 22 hour BP components except for night and day BP behavior with a greater reduction in the circadian rhythm leading to a significant increase of the second day n/dSR (1.01±0.12 vs 0.95±0.10, $p=0.02$, Figure 1) among patients with abnormal as compared to those with normal ABI. Moreover, patients with abnormal ABI showed significantly higher systolic (19.1±7.3 vs 14.6±4.6, $p=0.002$) and diastolic (14.0±6.3 vs11.4±4.6,$p=0.048$) BPV during the second night of registration.

When we analyzed the relationship between ABI measurements and BP variations (Table 2), patients with normal ABI, showed an increase in systolic ($p< 0.001$) and diastolic ($p<0.02$) BP during the second respect to the first day without differences in n/dSR. At variance, patients with abnormal ABI, showed a significant increase in n/dSR ($p<0.02$) while mean BP values were similar during the two days (Table2). As for AASI there was no difference between the first and second interdialityc day in the whole study group as well as in the subgroup with normal ABI, while patients with abnormal ABI showed a significant increase in AASI during the second as compared to the first interdialytic day ($P=0.006$) (Table 2).

When patients were stratified on the basis of n/dSR, those with n/dSR >1 during day 1 (risers in day 1, n=18) showed clinical and laboratory parameters substantially super imposable to the rest of the study-group except for significantly higher ProBNP and AASI. Moreover, patients with n/dSR >1 during day 2 (risers in day 2, n=34) where older, showed significantly higher ProBNP, and AASI and lower serum uric acid (6.37±1.14 vs 6.91±1.23, p= 0.02) and serum albumin (3.66±0.42 vs 3.90±0.31, p= 0.007) and were more likely to have left ventricular hypertrophy (p= 0.047) and abnormal ABI (0.006) as compared to those with a lower n/dSR (Table 3).

Logistic regression analysis showed that in the presence of abnormal ABI the risk of being a riser in day 2 was three times higher (OR 3.2, 5 95%IC 1.10-9.57, p= 0.03) even after adjusting for parameters of stiffness (AASI above the median: OR 3.33, 95% IC 1.15-9.66, p=0.03) and volume overload (NT ProBNP above the median: OR 1.94, 95% IC 0.68-5.59, p=0.7).

Discussion

In this study we used 44-hrs ABPM to assess interdialytic BP behavior in 81 HD patients and investigate its relationship with the presence of PAD and other factors which may reflect the interaction between vascular stiffness and volume status.

Overall, in the second inter-dialytic day, a time-period usually characterized by a more pronounced increase in blood volume as compared to the first one, we recorded an increase in all BP components, namely systolic, diastolic, and pulse pressure.

The presence of atherosclerotic damage had a considerable influence on the circadian BP rhythm. In fact, ABI-detected peripheral vascular abnormalities were associated with a progressive attenuation of nocturnal BP fall as indicated by the increased n/dSR in the second day when most patients became reverse dippers. Furthermore, we found that, in the second day of ABPM, vascular stiffness as assessed by AASI was significantly greater and BPV was increased during nighttime in patients with abnormal ABI.

While the circadian rhythm in systolic and diastolic BP in HD patients has previously been the object of several investigations (14), pathogenetic factors and mechanisms underlying this complex clinical feature remain at present poorly defined. Previous reports demonstrated blunted nocturnal decline of BP in a significant number of HD patients (11, 14-15) even when normotensive (16). The reason for these findings are probably multifactorial (17-20) and possible mechanisms include volume overload (19), autonomic dysfunction (21), decreased physical activity (22), sleep disordered breathing (23), or abnormalities in several hormonal and neuroendocrine mediators (catecholamines, renin, aldosterone, insulin, atrial natriuretic peptide, asymmetric dimethylarginine, parathormone) (17).

As a matter of fact, while interdialytic weight gain has been associated with concomitant BP rise, this relationship has not been consistent in all HD populations, especially when investigated by ABPM (24).

In line with data suggesting that inter-dialytic weight gain has little influence on average BP values, our logistic regression analysis suggests that the reverse dipping status is somewhat related to increments in arterial stiffness much more than to volume status. Accordingly, Agerwal and Light (11), reported that average BP levels and a blunted circadian amplitude of systolic and pulse pressure were related to increased aortic pulse wave velocity in a large population of HD patients suggesting that BP behavior in HD patients is mainly influenced by increased stiffness rather than by interdialytic weight gain.

Nevertheless, this is the first time, to the best of our knowledge, that BP components during interdialytic interval has been described in patients with PAD. In particular, we found that a blunted nocturnal BP decline is associated to the presence of abnormal ABI during the second interdialytic day.

Our data confirm previous studies indicating that ABI, assessed by oscillometric BP monitor may be an easy to use, low cost tool to identify high risk patients on HD (25).
Moreover, the present data build on previous findings indicating that patients with abnormal ABI not only show an unfavorable clinical and bio-humoral risk profile, i.e. a history for cerebral and peripheral vascular disease, worse glyco-metabolic parameters, and indirect signs of malnutrition but also a blunted circadian BP profile with reverse dipping status and indirect signs of increased stiffness (i.e., AASI and BPV) during the second interdialytic day. These results indicate that in patients with atherosclerotic damage a reduction in arterial cushioning function becomes more evident as extra-cellular volume increases overtime (i.e. during the second interdialytic day). The lack of relationship we found between these hemodynamic modifications and average BP level in patients with abnormal ABI , at variance with what has been observed in patients with normal ABI (Table 2), might be due to a more intensive antihypertensive treatment in the former. Pharmacologic treatment, in fact, may have flattened the interdialytic rise in arterial pressure without impacting on arterial stiffness.

The independent predictive role of n/dSR>1 has been previously reported (16,26) in HD patients. Accordingly, the reverse dipping status in the second day (44%) is associated in our patients with a worse biohumoral and clinical profile characterized by increased proBNP, parameters of malnutrition, AASI and an higher prevalence of abnormal ABI (Table3). Taking into consideration the haemodynamic and global complexity of HD patients, our data support the notion that a longer ABPM recording is more informative than the traditional 24hrs one. Our findings are at variance with those of Tripepi et al. (10) and Santos et al. (16) who were unable to show any between-day variation in BP profile. This is possibly due to differences in studies' objects and in clinical characteristics of patients subgroups, as we specifically aimed at addressing the relationship of atherosclerotic peripheral diseases and BP behavior.

There are some limitations to our work that must be acknowledged. First, its cross-sectional nature does not allow us to infer a causal relationship between observed findings. Moreover, data on interdialytic weight gain which would have contributed to strengthen our interpretation of study results, were not available for analysis. On the other hand, this study provides 44h-ABPM data in a large group of HD patients managed according to current best clinical practice and is representative of CKD population undergoing HD treatment as for age, common etiologies of ESRD, duration of HD

sessions, and prevalence of poorly controlled hypertension. Thus, this study lends itself as a useful database for clinical and research reference.

In conclusion, our study provides the first evidence that pathological ABI is associated with an abnormal circadian BP behavior in HD patients. These findings may help clarify the pathophysiological mechanisms leading patients with abnormal ABI to a poorer survival rate and support a wider application of this simple and noninvasive test for PAD screening. In addition, the relationship of a blunted or reversed circadian BP rhythm with atherosclerotic peripheral disease provides an explanation for the worse outcome recently reported in HD patients with n/dSR abnormalities and strengthens the importance of a more diffuse application of 44-h ABPM to improve the identification of high risk patients.

Transparency declarations: None to declare

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Tables headings

Table 1. Demographic, clinical and routine pre-dialysis laboratory parameters of study subjects, overall and on the basis of ABI measurements

Table 2. Interdialytic ABPM measurements on the basis of ABI determination

Table 3. Demographic, clinical and ABPM parameters of study subjects, on the basis of n/dSR during the two interdialytic days

Legend to figure

Figure 1. ABPM derived SBP night/day ratio in patients with and without ABI abnormalities