Pulse pressure, renal function and mortality in hospitalized Congolese patients with arterial hypertension

M'buyamba-Kabangu JR*,

Disashi T**, Biswika RT**, Kayembe PK***, Buila NB*, Lepira BF****

Correspondence:
Professeur Dr JR M'Buyamba-Kabangu, *MD, PhD*
Hypertension Unit, Division of Cardiology
Department of Internal Medicine / UNIKIN
PO Box 123, Kinshasa XI, DR Congo
Phone +243 9999 44232; E-mail: jerembu@yahoo.fr

Résumé

***Objectif*:** Evaluer la fonction rénale et la mortalité totale des malades Africains hospitalisés pour diverses conditions liées à l'hypertension artérielle.

Méthodes: A l'admission des 401 malades hypertendus consécutifs (129 femmes, 118 nouvellement diagnostiqués et 157 sous traitement antihypertenseur), nous avons mesuré la pression artérielle, le pouls, le poids, la taille et le tour de taille, obtenu l'histoire médicale, la notion d'alcoolisme et de tabagisme, et déterminé le taux d'hémoglobine et de créatinine sérique. Nous avons enregistré l'issue vitale a la sortie de l'hôpital en termes de décès ou de survie. Nous avons calculé l'indice de masse corporelle et estimé le taux de filtration glomérulaire (eTFG) standardisé a 1,73m² selon les formules disponibles, et défini l'hypertrophie ventriculaire gauche par l'amplitude de l'onde R en aVL ≥1,3 mV.

***Résultats*:** L'âge moyen des patients était de 54 ans avec une pression de 178, 106 et 72 mmHg respectivement pour la systolique, la diastolique et la pression pulsée. Leurs poids, taille, tour de taille et indice de masse corporelle se chiffraient respectivement à 68 kg, 169 cm, 98 cm et 24,4 kg/m². Ils présentaient 11,4 g/dl d'hémoglobine, 112 mg/dl de glycémie et 82 ml/min/1,73m² d'eTFG. Aucun patient n'avait une pression < 140/90 mmHg a l'admission. La maladie rénale chronique (définie par un eTFG < 60 ml/min/1.73 m²) était chez 47 patients (11,7%), dont 8 (6,8%) parmi les hypertendus nouvellement diagnostiques, 24 (19%) parmi les malades non traités et 15 (9,6%) sous traitement antihypertenseur. La maladie rénale chronique prédominait parmi les diabétiques et les patients avec obésité abdominale et présentait une proportion moindre d'hypertrophie ventriculaire gauche. eTFG était positivement corrélé au taux de l'hémoglobine et inversement corrélé à l'âge, à la pression artérielle, à la durée connue de l'hypertension et au taux de glycémie en considérant l'ensemble des malades, ou séparément les patients nouvellement diagnostiqués ou ceux ayant la maladie rénale (P<0,05). L'association entre eTFG et la pression pulsée a persistée après ajustement pour l'âge, le sexe, la glycémie et la durée de l'hypertension. 89 décès (22,2%), ont été enregistrés au cours de l'hospitalisation. La mortalité des patients avec maladie rénale (n=36; 76,6%) était plus élevée (P<0,0001) comparativement aux patients avec fonction rénale normale (n=53; 17,6%). Par comparaison aux survivants, le taux de filtration glomérulaire était plus faible alors que la pression pulsée était plus élevée chez les patients avec maladie rénale décédés. Plus forte parmi les diabétiques et les patients avec obésité abdominale, la mortalité était moindre parmi les malades sous traitement antihypertenseur à l'admission.

***Conclusion*:** Les résultats indiquent que la pression pulsée est un déterminant indépendant de la sévérité de la détérioration de la fonction rénale et de la mortalité chez les patients noirs avec hypertension artérielle.

***Keywords*:** Pression pulsée**,** fonction rénale**,** mortalité, hypertension, Africains.

* Hypertension Unit, Division of Cardiology, Department of Internal Medicine, University of Kinshasa (Unikin) Hospital, Kinshasa, ** University of Mbujimayi, Fondation Cardinal Malula, Mbujimayi and *** School of Public Health, University of Kinshasa (Unikin), Kinshasa, DR Congo, **** Service of Nephrology, Department of Internal Medicine, University of Kinshasa (Unikin) Hospital, Kinshasa

SUMMARY

Objective. To assess renal function and mortality in African patients hospitalized for hypertension-related disorders.

Methods. Blood pressure, weight, height, pulse rate, waist circumference, medical history, tobacco and alcohol habits, plasma glucose, blood hemoglobin and serum creatinine were obtained on admission and the outcome (death or survival) was recorded at discharge in 401 consecutive hypertensive patients (129 women, 118 newly diagnosed, 157 on current antihypertensive medication). Body mass index and eGFR were computed according to published formulas. R wave voltage ≥1.3 mV in lead aVL on a 12 lead ECG defined left ventricular hypertrophy.

Results. Average values were 54 years for age, 178, 106 and 72 mmHg for systolic, diastolic and pulse pressure, 68kg for weight, 169cm for height, 24.4kg/m² for BMI, 98cm for waist, 11.4 g/dl for hemoglobin, 112mg/dl for plasma glucose, and 82ml/min/1.73m² for eGFR. In no patient was BP < 140/90 mmHg on admission, chronic kidney disease (CKD) with eGFR below 60 ml/min/1.73 m² was observed in 47 patients (11.7%), 8 of whom (6.8%) were naive patients, 24 untreated (19%) and 15 (9.6%) on antihypertensive medication. CKD predominated among diabetics and those with central obesity whilst LVH was shown in fewer CKD patients. eGFR was positively correlated to blood hemoglobin and inversely to age, blood pressure, known duration of hypertension and plasma glucose level in the whole study population, in naive patients and in those with CKD taken separately (all p<0.05). The association between eGFR and pulse pressure persisted after adjustment for age, gender, plasma glucose and duration of hypertension. 89 deaths (22.2%), occurred during the hospitalization period. Mortality was higher (p<0.0001) in CKD patients (n=36; 76.6%) than in those with normal renal function (n=53; 17.6%). eGFR was lower in CKD deceased patients whose pulse pressure was higher compared to survivals. Mortality was higher in CKD patients with diabetes or central obesity; it was lower in those on antihypertensive treatment at admission.

Conclusion. The present data indicate that pulse pressure is an independent determinant of the severity of renal function deterioration and outcome in black patients with arterial hypertension.

***Keywords*:** Pulse pressure**,** kidney function, mortality, hypertension, Africans.

Introduction

Alterations in the homeostatic mechanisms that lead to elevation of blood pressure (BP) do imply the participation of the kidney (1, 2). BP starts to rise once the kidney requires higher than usual level of BP to ensure adequate urinary excretion of sodium to maintain extracellular volume within normal limits (1).

Chronic renal dysfunction (CKD) appears to be a deadly condition that accompanies and is often aggravated by elevated BP (3, 4) although the causal role of benign essential hypertension in initiating kidney damage has been questioned (5, 6). To this regard, Blacks seem to shoulder a disproportionately high burden of kidney disease when compared to other ethnic groups in the setting of hypertension (7-9). Studies of polymorphisms in genes encoding for components of BP regulating systems have identified alleles that are associated with changes in renal function in some populations (10). It has been postulated that the elevated prevalence of cardiovascular risk factors such as obesity and diabetes are major contributors to the high burden of CKD in African-Americans (11). The situation for sub-Saharan Africans could be different and pernicious environmental conditions like poverty, infections, and poor health habits might exert a deleterious influence. We therefore investigated determinants of kidney function deterioration and severity among African patients living in relatively poor health conditions who were hospitalized for hypertension-related disorders.

Methods

The present work reports on 401 consecutive Congolese patients admitted and followed up at Dipumba and Bonzola Hospitals (Minière de Bakwanga, (MIBA), Mbujimayi, DR Congo), during the period 2001-2003 for hypertension-related disorders (12). Information on age, gender, smoking and alcohol use, known duration of hypertension, current antihypertensive medication, history of chronic diseases is analyzed along with clinical and biological data obtained on patient admission. The outcome at discharge in term of death or survival is also considered in the analysis. BP was measured in recumbent position with a mercury sphygmomanometer and the average of two measurements is reported. Pulse pressure (PP) was calculated as the difference between systolic and diastolic pressure. Pulse rate was counted over one minute on the radial artery. Body weight and height were used to compute the body mass index (BMI) as the ratio of weight (kg) to the square of height (m^2); BMI$\geq$ 25 kg/m^2 defined overweight/obesity. Blood hemoglobin, fasting plasma glucose and serum creatinine were determined routinely. Estimated glomerular filtration rate (eGFR) standardized to 1.73 m^2 of body surface area was calculated using the MDRD (13) following formula: 186.3 × (serum creatinine in $mg/dl^{-1.154}$) × (age in $years^{-0.203}$) × 1.212 (our patients are blacks) × 0.742 (if female patient) and, according to recent guidelines (14, 15). CKD was defined as an eGFR below 60 ml/min/1.73 m^2. A 12 leads ECG record was obtained in most patients and R wave voltage $\geq$ 1.3 mV in lead aVL was used to define left ventricular hypertrophy (LVH).

Statistical analysis

Data are represented by means ± SD, median and range or frequencies and percents where appropriate. Groups were compared by means of Student t test, Chi square test or one-way analysis of variance (Anova) with Scheffé's test for multiple comparisons. Single regression coefficients were obtained using Pearson's correlation

matrix. In multivariate analyses we assessed the independent determinants of eGFR by stepwise linear regression and modeled the probability of death in CKD patients using stepwise logistic regression. A probability of 5% or less was considered statistically significant.

Results

Chronic kidney disease

The present series comprised of 401 consecutive hypertensive patients of whom 129 (32.2%) were women, 118 (29.4%) naive patients and 157 patients (39.2%) reporting current use of antihypertensive medication. However, on admission no patient had BP below 140/90 mmHg. LVH, hypertensive retinopathy, stroke, congestive heart failure, hypertensive encephalopathy and CKD were the most frequent complications with a share of at least ten patients each. Table 1 summarizes the characteristics of patients with (n=47; 11.7%) and without CKD (n=354; 88.3%).

Table 1. General characteristics of patients according to CKD

	With CKD	Without CKD	All patients
N	47	354	401
Age (years)	53 ± 10	54 ± 9	54 ± 9
Weight (kg)	73 ± 8	68 ± 7***	68 ± 7
Height (cm)	168 ± 7	168 ± 5	169 ± 6
BMI (kg/m²)	25.9 ± 3.4	24.0 ± 2.2***	24.2 ± 2.4
Waist circumference (cm)	97 ± 10	94 ± 8**	94 ± 8
Systolic pressure (mmHg)	197 ± 19	176 ± 15	178 ± 9
Diastolic pressure (mmHg)	110 ± 9	105 ± 10	106 ± 7
PP (mmHg)	77 ± 6	71 ± 10***	79 ± 6
Pulse rate (beats/min)	87 ± 15	76 ± 9	76 ± 9
Hypertension duration (years)[a]	7	6	6
Hemoglobin (g/dl)	10.1 ± 0.8	11.8 ± 1.1***	11.8 ± 2.3
Plasma glucose (mg /dl)	151 ± 59	106 ± 25***	112 ± 8
Serum creatinine (mg /dl)	2.26 ± 0.50	1.05 ± 0.12***	
eGFR (ml/min/1.73 m²)	54 ± 6	98 ± 8***	82 ± 7

Values are means ± SD or [a] median. eGFR = estimated Glomerular Filtration Rate
**p<0.01; ***p<0.001

Average body weight, BMI, waist circumference, systolic BP, PP, plasma glucose, serum creatinine were higher whereas blood hemoglobin and eGFR were lower in CKD patients (all p<0.05). The proportion of patients with CKD significantly increased from 6.8% (n=8) in naive patients to 12.9 % (n=21) and 15% (n=18) in those with hypertension duration <10 years or ≥10 years, respectively. Among the CKD patients 29 (61.7%) and 18 (38.3%) had eGFR of 30-59 ml/min/1.73 m² (CKD stage 3) and 15-29 ml/min/1.73 m² (CKD stage 4), respectively; no patient had eGFR level below 15 ml/min/1.73 m². CKD predominated (p<0.001) among diabetics (n = 30; 35.3%) than non diabetics (n=17; 5.4 %) and among patients with (n=23; 22.8 %) than without central obesity (n-24; 8 %) whilst fewer (p<0.001) CKD patients had ECG evidence of LVH (n = 7; 4.2% *vs* 40; 17.1 %). Gender distribution and the proportions of smokers, alcohol drinkers and patients on treatment at admission were similar in those with and without CKD (Table 2).

Table 2. Risk factors among patients with and without CKD

	With CKD n (%)	**Without CKD** n (%)	***p***
Gender (males/females)	29 (61.7)/18 (38.3)	243(68.6)/111 (31.4)	Ns
Smokers	8 (17.0)	55 (15.5)	Ns
Alcohol users	27 (54.4)	216 (61)	Ns
Overweight/obesity	24 (51.1)	79 (22.3)	<0.001
Central obesity	23 (48.9)	78 (22)	<0.001
Left ventricular hypertrophy	7 (14.9)	180 (50.8)	<0.001
Diabetes	30 (63.8)	56 (15.8)	<0.001
Awareness of hypertension	39 (83)	244 (68.9)	<0.05
Treatment of hypertension	15 (31.9)	142 (40.1)	Ns

CKD: chronic kidney disease; NS: Not significant

In single regression analysis eGFR was positively correlated to blood hemoglobin and negatively (all p<0.05) to age, duration of hypertension, plasma glucose, systolic BP, diastolic BP and PP for the whole study population, for naïve patients and for those with CKD taken separately (Table 3). The relationship between eGFR and PP (Figure 1) persisted after stepwise multivariable adjustment (Table 4).

Table 3. Correlation coefficients of estimated glomerular filtration rate and other variables

	All patients	Newly diagnosed	CKD patients
Age	-0.37**	-0.52**	-0.19
BMI	-0.18**	-0.14	-0.05
Waist	0.09	0.09	0.52**
DBP	-0.16*	-0.34**	-0.06
SBP	-0.43**	-0.51**	0.27
PP	-0.48**	-0.42**	-0.38**
Hemoglobin	0.46**	0.37**	0.08
Glycaemia	-0.32**	-0.23*	0.16

* p<0.05; **p<0.01.

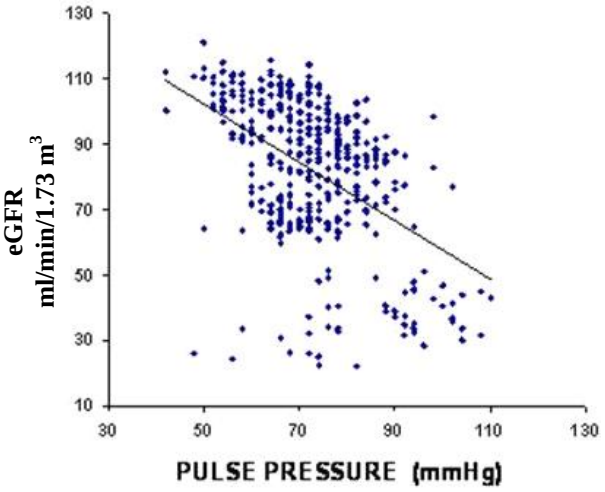

Figure 1. Relationship between eGFR and pulse pressure

Table 4. Partial correlation coefficients of eGFR and other variables

Variable	**B**	**p**	**R^2**	**p**
Constant	147.1			
PP	-0.69	<0.001		
Age	-0.53	<0.001		
Plasma glucose	-0.16	<0.001	0.45	<0.001
BMI	-2.54	<0.001		
Waist	1.02	<0.001		
HT Duration	-0.28	0.04		

PP: pulse pressure; BMI: body mass index; HT: hypertension

Mortality in CKD patients

During the median hospital stay of 15 days (range 1 – 64 days), 89 deaths (22.2%) were recorded 36 of whom (40.4%) occurred among CKD patients. All-cause mortality was thus significantly higher ($p<0.0001$) in CKD patients (n=36; 76.6%) than in those with normal renal function (n=53; 17.6%). Average eGFR level in deceased CKD patients (31.2±7.3 ml/min/1.73 m^2) was lower as compared to survivals (45.5±6.3 ml/min/1.73 m^2). There were 21 deaths (72.4%) in CKD stage 3 and 15 (83.3%) in CKD stage 4 patients, respectively. Among the CKD patients, the number of deaths amounted to 28 (93.3%) in diabetics, 21 (91.3%) in those with central obesity and 7(46.7%) in patients untreated on admission. Using logistic regression analysis with deaths in CKD patients as dependent variable, no factor emerged as a significant predictor of the outcome; the trends shown by gender, duration of hypertension, presence of diabetes or central obesity, and treatment status at entry were not significant (Table 5).

Table 5. Determinants of death in CKD patients

Variable	*p*	Odd ratio	95% c.i.
Gender	0.090	9.603	0.700 - 131.77
Pulse pressure	0.198	0.933	0.839 - 1.037
Tobacco	0.99	2.76 E02	0.000 - 1.0034
Alcohol	0.283	4.779	0.276 - 82.645
Central obesity	0.065	16.925	0.834 - 343.28
Diabetes	0.070	0.11	0.000 - 1.448
HT duration	0.051	63.178	0.986 - 4048.9
Plasma glucose	0.151	17.313	0.352 - 851.98
Treatment	0.090	0.022	0.000 - 1.808
LVH	0.543	0.367	0.014 - 9.279
Constant	0.399	37.538	

HT: hypertension; LVH: left ventricular hypertrophy; CI: coefficient interval

Discussion

An elevated mortality rate associated with CKD in hospitalized hypertensive African patients was the key finding of the present work. CKD affected 11.7 % of the series in whom all-cause mortality was significantly higher than among the patients with normal renal function. The higher mortality rate in the CKD patients was associated with diabetes mellitus, central obesity, and absence of antihypertensive treatment on admission. On average, eGFR level was lower in deceased CKD patients as compared to survivals suggesting a much gloomy prognosis for patients with poorer renal function.

The prevalence of renal dysfunction observed in the present study agrees with the literature. Indeed, in a cohort of 787 essential hypertensive patients attending a hospital clinic, an estimated creatinine clearance less than 60 ml/min was found in 14% (16). The prevalence of renal dysfunction in patients with long-standing hypertension is significantly greater as compared with that found in community-based studies (17).

Our rate of kidney function deterioration and the subsequent appalling mortality lend support to the reported high vulnerability of black subjects to hypertension-induced renal damage. In no case was hypertension a controlled condition in the present series. On the admission, CKD had already developed in a substantial proportion even in the naïve patients. This observation indicates delayed presentation of patients probably due to asymptomatic course of hypertension. It mostly confirms that Blacks do shoulder a heavy burden of renal dysfunction in the setting of arterial hypertension (7-9, 18-21). Compared to Caucasians, Blacks whose high BP began in childhood presented higher rates of micro-albuminuria in adulthood (22). Likewise, African-Americans with mean BP above 98 mmHg displayed a greater risk of end stage renal failure than whites (23). Finally, the major fraction of Blacks undergoing chronic dialysis suffers from diabetes and / or hypertension induced renal failure (24, 25). Such a kidney vulnerability is thought to lay in altered renal autoregulation probably linked to a large abnormality of the endothelial function (26, 27); it is worsened by various conditions including hypertension and insulin resistance syndromes (26).

Average BP, body weight, waist circumference and plasma glucose levels were higher in patients with than without CKD. The inverse relationship between PP and eGFR suggests on one hand that the probability of CKD was greater in patients with higher PP on admission, and that altered arterial distensibility might have participated to the kidney damage on the other hand. PP is a well established risk factor for cardiovascular (28) and renal damage (29), especially in the aged (30) with ambulatory PP bearing to this regard an even greater predictive value (29). Given the average age of our patients, the deleterious effect of elevated PP (and elevated BP in general) appears to occur precociously in black sub-Saharan African patients. However, altered kidney function is known to attenuate BP response to antihypertensive therapy and could have been both the cause and the consequence of poorly controlled hypertension (28).

In multiple regression analysis: gender, age, PP, duration of hypertension and plasma glucose yielded significant partial coefficients with eGFR. Aging

often leads to development of isolate systolic hypertension that surely increases PP. CKD patients who deceased had on admission higher PP than the survivors corroborating the gloomy prognosis of altered arterial compliance and its pernicious effect on cardiovascular (28-30) and renal mortality (31,32). Aging goads a progressive decline in the number of nephrons that at least partly accounts for the decrease in blood hemoglobin with the potential to affect cardiovascular system (33). However, the impact of this CKD associated anemia on mortality in the present work has not been specifically assessed.

Our results showed no difference in exposure to tobacco or alcohol use among patients with and without CKD. High plasma glucose level emerged as an independent determinant of eGFR and thus, of kidney dysfunction. Despite the absence of A1cHb, the elevated plasma glucose levels appear likely imputable to uncontrolled diabetes. It could also be related to the state of insulin resistance associated or induced by kidney dysfunction. Greater BMI and waist circumference observed in CKD patients appear in accordance with other reports where an elevated risk to develop kidney dysfunction was associated with increased BMI.[34] Maintaining ideal body weight is believed to reduce the risk of cardiovascular disease and to slow the rate of kidney function deterioration although in the setting of chronic heart failure or chronic dialysis a negative association characteristic of reverse epidemiology (35,36) has been demonstrated between BMI and cardiovascular or renal events.

The elevated all-cause mortality in our CKD patients is corroborative of previous reports in most population-based studies (37, 38) as well as in hypertensive patients (39-41). Mortality in CKD patients predominated among those with diabetes mellitus, untreated hypertension on admission, elevated plasma glucose and central obesity. In the logistic regression analysis however, the study lacked sufficient power to demonstrate significant predictive effect of any of the variables considered in the model on mortality that occurred in CKD patients. A pejorative trend was observed with male gender, longer hypertension duration and central obesity and a protective one was exhibited by the presence of diabetes and the use of antihypertensive treatment on admission. Both trends were short of significance. The trend observed with diabetes advocates reverse epidemiology whereas that shown by antihypertensive treatment might reflect to some extent the fact that in no patient treatment had resulted in BP normalization.

Our study has limitations. First, the definition of CKD was based on a single serum creatinine determination obtained on admission with the potential to misclassify renal status in those with transient rather than chronic renal dysfunction. Repetition of measurement was not affordable by the majority of patients who bore themselves all the health care cost. Moreover, the range of the hospitalization stay (1-64 days) precludes compliance with the three months considered mandatory in the guidelines (15). Second, we only assessed all-cause mortality in our patients and could not establish the specific causes of death. All-cause mortality is an objective parameter not subject to misclassification. The mean value of the eGFR in our deceased CKD patients suggests that uremia was probably not a major cause of mortality. Instead, the cardiovascular

complications resulting from mild renal dysfunction might be incriminated (42, 43). Third, our patients were surely selected and therefore extrapolation of data to all hypertensive patients is not warranted. Finally, we only considered in the analysis the treatment status prior to admission. The extent to which in-hospital treatment has affected the outcome remains unsettled.

In conclusion, the present data indicate that chronic kidney dysfunction is a frequent complication of the hypertensive process in which alteration in arterial stiffness is implicated. The components of the metabolic syndrome, diabetes, central obesity and aging seem to worsen the outcome on which antihypertensive therapy bears a beneficial effect.

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