Original Article

Haemodynamic changes and peripheral vascular characteristics associated with pathophysiological alterations in Preeclampsia patients at the University Teaching Hospital, Lusaka, Zambia

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ABSTRACT

Background: The circadian blood pressure changes in pregnancy are poorly documented though the severity of hypertensive disorders especially in pregnancy is said to be better detected by 24hour blood pressure monitoring. The contribution of peripheral vascular variations to these alterations is yet to be elicited. The association of these changes to the renal pathological dysfunction is also not fully understood.

Materials and method: Ambulatory blood pressure measurements and kidney function tests (i.e. creatinine, protein, sodium and uric acid) were done in patients admitted to UTH for hypertension in second and third trimesters of pregnancy. The Complior was used to determine the pulse waveform, pulse wave velocity (PWV) and augmentation index (Aix) as surrogate parameters for peripheral vascular compliance.

Results: Twenty-six (26) women, between 22-42 years old and 24-36 gestational weeks, participated in this study. The majority of our population were either non- or reverse dippers (91.6%). The type A pulse waveform was dominant in all three groups indicating endothelial dysfunction. Dippers had a higher creatinine concentration in both urine and serum and uric acid in serum than non-dippers (7.051mmol/24hrs; 108.703µmol/L;0.507mmol/L; respectively $p<0.0001$).

The observed association of diurnal variations in hemodynamic parameters and dipping status indicates significant vascular pathology that may herald these individuals' increased risk of cardiovascular complications. The dominance of the type A pulse waveform in this population is indicative of significant endothelial dysfunction.

Conclusion: The association seen between elevated blood pressure readings and proteinuria indicates a possible common pathophysiological process that leads to increased porosity at the glomeruli.

INTRODUCTION

Variations of hemodynamic and peripheral vascular characteristics have been reported in both healthy and complicated pregnancies [1]. The circadian rhythm of blood pressure characterized by a nocturnal dip of greater or equal to 10%, a phenomenon said to result from endogenous circadian patterns in autonomic nervous and related endogenous systems, has been reported in normotensive pregnancies. Normotensive pregnancies are supposed to follow this biological clock with the highest blood pressure readings recorded early in the morning, afternoon, or late in the afternoon and the lowest recordings in the night.

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Typically, persons with a 10-20% dip between day and night blood pressures are referred to as dippers. However, this pattern is lost in persons who are termed non-dippers, and in some instances, there may be a reversal of the phenomenon, where the blood pressure rises instead (reverse dippers). This has been reported in patients with essential hypertension [2]. It is further stated that changes in the circadian rhythm are a better indicator of the severity of hypertension than the conventional method of blood pressure monitoring [3,4,5]. Non-dippers, in comparison to dippers, are said to be at a higher risk of cardiovascular disease and target organ damage [1, 4]. This phenomenon has not been well articulated in patients with preeclampsia.

Preeclampsia, with a reported incidence of 0.5-3% in Sub Saharan Africa [6], is considered to be more than just a hypertensive disorder but a systemic syndrome [7]. Several pathophysiological alterations have been associated with the development of this condition, including endothelial dysfunction that causes decreased arterial compliance (arterial stiffness), resulting in increased peripheral resistance that manifests in increased arterial blood pressure and pulse wave velocity. Studies have shown that arterial stiffness remains either unchanged or decreases amongst pregnant women when compared with non-pregnant women but may increase significantly in hypertensive women [8].

The alterations in endothelial function are said to be better appreciated in the velocity and character of the arterial pulse wave as it moves from the carotid artery through the brachial arterial (CR) or the femoral artery (CF). As the endothelial dysfunction increases, the pulse wave velocity (PWV) increases, and the pulse waveform is said to change from a C-type wave to an A-type wave. While these alterations have been reported in several studies in essential hypertension, we have been among the very few who have published similar findings in our previous publication of work done in black African patients of pregnancy-induced hypertension (PIH) at the UTH, Lusaka [8].

The causation of endothelial dysfunction leading to the proteinuria in preeclampsia is said to be associated with endothelial damage [9]. We postulate that the rise in blood pressure imposes excessive filtration pressure on the glomerular capillaries, which leaks the protein. However, there has been no study that has shown an association between the rise in BP and the degree of proteinuria.

This study aimed to investigate alterations in the characteristics and velocity of the arterial pulse waves in the preeclamptic black population and mainly aimed at investigating the diurnal hemodynamic variations (Blood Pressure and Heart Rate) in these patients to document the possible association between these alterations and the severity of proteinuria.

METHODOLOGY

Women with a diagnosis of PIH and admitted to UTH by the attending obstetrician (blood pressure above 140/90mmHg, gestational age of above 20 weeks, between 18-45 years with no known cardiovascular pathology presenting to the UTH department of obstetrics and gynaecology) were recruited using sequential sampling into this minimal risk study. Sociodemographic data were collected, including obstetric history. Weight and height were measured to the nearest 0.1kg with a calibrated Seca scale and the nearest 0.1cm with a stadiometer, respectively. Participants were allowed to rest for 15 minutes before blood pressure readings were measured using an Omron M6 comfort automatic BP monitor. Three readings were taken spaced by 2-5 minutes, and the average of the last two readings was chosen for the record. Using the Complior (ALAM, France), measurements were made by applying non-invasive probes on the surface of the skin over the carotid and radial arteries to obtain the crPWV, Augmentation Index (Aix) and central blood pressure readings. Participants were not allowed to move, speak, or sleep during the measurements.

Urine was collected for a total period of 24 hours and tested for creatinine, sodium, and protein. Blood samples were also collected halfway through the urine collection and tested for creatinine, sodium, uric acid, and urea. Blood pressure recordings were automatically measured every 15 minutes during the day and every 30 minutes in the night using an ambulatory blood pressure machine (ABPM) (Diasys Integra II, Novacor).

Stata version 15 was used for all statistical analyses. Data were categorized into dipping statuses, i.e., non-dippers, dippers and reverse dippers using this formula; % dipping BP = (mean daytime BP-mean night time BP)/mean daytime BP *100

Mean, and proportions were made using Kruskal Wallis tests.

We also performed a multiple regression analysis from the panel data which were measured to investigate the relationship between mean arterial pressure and systolic and diastolic blood pressures, heart rate, creatinine, protein, and sodium levels in urine and uric acid and creatinine in blood, augmentation index and pulse wave velocity. Hausman test was used to determine the best model for this dataset. Research Ethics approval was obtained from the University of Zambia Biomedical Research Ethics Committee (UNZABREC).

RESULTS

A total of 26 patients participated in this study with a mean age of 31.3 years and gestational age of 29.71 weeks (Table 1). The mean blood pressure was 135/91 (SBP range 88-238; DBP range 48-148mmHg).

Table 1: Study Demographics

Characteristics	Mean	Range
Age (years)	31.30	22 - 42
Gestational age (weeks)	29.71	24 - 36
Height (cm)	158.75	147 - 170
Weight(kg)	75.46	48 - 97
Systolic blood pressure (mmHg)	135.15	88 - 238
Diastolic blood pressure (mmHg))	91.21	48 - 148
Mean arterial pressure (mmHg)	105.74	64 - 168
Heart rate (beats/min)	88.12	48 - 150

Table 2: Biochemical measurements

Parameter	Mean	Range	Normal range
Urine creatinine	8.79mmol/24hr	2.7-17.5mmol/24hr	5.30-15.9mmol/24hr
Serum creatinine	72.079µmol/L	46-178µmol/L	53-97µmol/L
Uric acid	0.399mmol/L	0.23-0.69mmol/L	0.14-0.39mmol/L
Sodium concentration	52.58mmol/24hr	16-107mmol/24hr	40-220mmol/24hr
Urine protein	1.94g/24hrs	0.18-9.63g/24hrs	<0.15g/24hrs
CRPWV	9.90m/s	3.5-12.8m/s	5-13m/s*
Aix	11.15	-93.5-99.87	-21-23*

* Normal levels were taken from Kaluba, *et al*., 2015

Urine creatinine and serum, uric acid, and sodium were in normal ranges in this population (Table 2). Urine protein was higher as expected in most of the patients. A mean crPWV was 9.90m/s (3.5-12.8m/s) and the Aix mean was 11.15 (-93.5-99.87).

We performed a multiple regression model to investigate associations between the biochemical markers measured and mean arterial pressure (Table 3).

Table 3: Association model of mean arterial blood pressures to measured biochemical parameters

Mean	Degrees of freedom	F value	P-value
Urine Creatinine	2	20.25	<0.001
Urine protein	2	86.12	<0.001
Urine sodium	2	95.48	<0.001
Serum Uric acid	2	22.63	<0.001
Augmentation index (Aix)	2	41.81	<0.001

The random effect model used. $\sigma = 11.662$ R^2 overall =0.266

Patients with higher MAP had higher levels of creatinine, protein, and sodium in the urine, a higher level of uric acid in serum and higher augmentation index (Aix) (p=<0.001). Creatinine in serum and crPWV was omitted from the model because it could not independently show association with MAP.

Diurnal Rhythm

Only 2 of the 23 patients (8.33%) were dippers, while 11(45.8%) were non-dippers, and 11 (45.8%) were reverse-dippers (Table 3). Hemodynamic characteristics between non-dippers and reverse-dippers were very similar and significantly different

from the dippers. While dippers had an average blood pressure of 126/91mmHg, non-dippers and reverse-dippers had significantly higher average blood pressure of 136/91 and 135/91 mmHg, respectively. It was the systolic blood pressure, which was significantly different amongst the three groups (p=<0.001), diastolic, and mean blood pressures were similar (p>0.05).

The dippers had a significantly higher mean heart rate (99 beats/min) than the non-dippers (88beats/min) and reverse dippers (86 beats/min) (p=<0.001). This may indicate a blunting of the sympathetic response in hypertensive patients.

Renal Function

Dippers had significantly more creatinine secreted in urine (7.05±1.46mmol/ml) compared to the non-dippers (5.64±3.08mmol/ml) and reverse dippers (5.24±2.47mmol)/24hrs, p<0.01) indicating a degree of renal dysfunction in the hypertensive patients. This was also reflected in the magnitude of protein excretion in this population. Proteinuria was higher amongst the non-dippers (2.56g/24hr) and reverse dippers (1.66g/24hr) as compared to dippers (0.19g/24hr; p<0.001). However, serum creatinine was significantly higher in dippers (108.70±65.63mmol/l) than in non-dippers (67.35±27.83 mmol/l) and reverse dippers (69.49±16.03 µmol/L). Sodium secretion was also twice as much in non-dippers (51.98mmol/24hrs) and reverse dippers (55.63mmol/24hrs) as compared to the dippers (24mmol/24hrs; p<0.001).

Serum uric acid was significantly higher in the dippers (0.51 ±0.60 mmol/l) compared to non-dippers (0.38±0.13mmol/l) and reverse dippers (0.40±0.11mmol/l). This was somewhat surprising as high uric acid levels have been traditionally reported in pre-eclampsia and eclampsia.

Table 4*: Biochemical markers stratified by dipping status*

	Dippers N= 2	Non-Dippers n= 11	Reverse-Dippers n=11	P-value
Urine creatinine conc. (du)	7.05	5.64	5.24	0.0001
Urine protein (g/24hr)	0.19	2.56	1.66	0.0001
Urine sodium (mmol/24hr).	24	51.98	55.63	0.0001
Serum uric acid (mmol/L)	0.51	0.38	0.40	0.0001
Serum creatinine (µmol/L)	108.70	67.35	69.49	0.0001

The significance level is 0.05. Kruskal Wallis test was used

Figure 1: Pulse wave velocity and pulse waveforms The dominant pulse waveform was the A-type for reverse dippers.

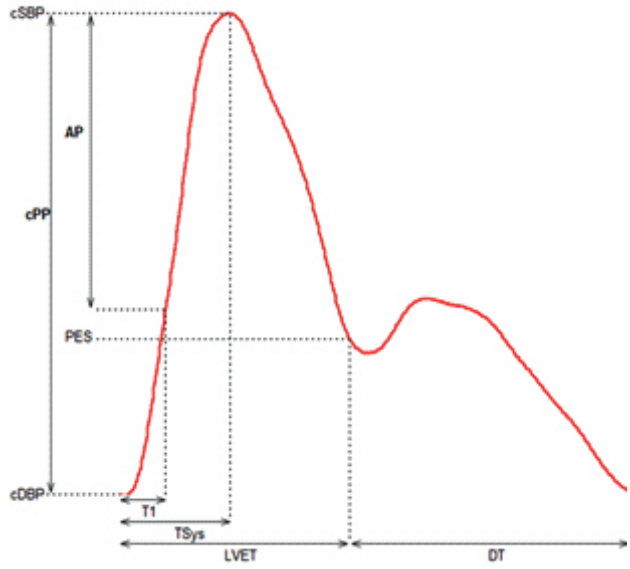

Figure 1: A recording of the pulse waveform (type A wave) by the Complior

cSBP=central systolic BP,cPP=central pulse pressure, cDBP=central diastolic BP, AP= augmentation pressure, PES= end-systolic BP, Tsys=timing of the systolic wave, T1= timing of the reflected wave, LVET= left ventricular ejection time, DT= diastolic time

Figure 2: The dominant pulse waveform was the C type for dippers.

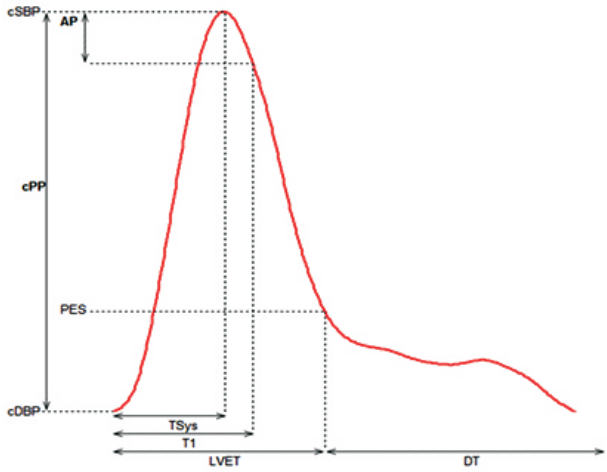

Figure 2: A recording of the pulse waveform (type C wave) by the Complior

cSBP=central systolic BP,cPP=central pulse pressure, cDBP=central diastolic BP, AP= augmentation pressure, PES= end-systolic BP, Tsys=timing of the systolic wave, T1= timing of the reflected wave, LVET= left ventricular ejection time, DT= diastolic time

The dominant pulse waveform was the A-type for non-dippers, and reverse-dippers (figure 3).

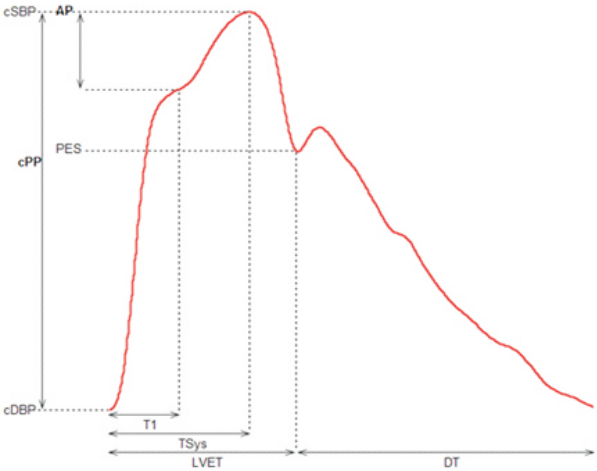

Figure 3: A recording of the pulse waveform (type A wave) by the Complior

cSBP=central systolic BP,cPP=central pulse pressure, cDBP=central diastolic BP, AP= augmentation pressure, PES= end-systolic BP, Tsys=timing of the systolic wave, T1= timing of the reflected wave, LVET= left ventricular ejection time, DT= diastolic time

DISCUSSION

The findings from this study reveal significant pathophysiological alterations in pregnancy-induced hypertension and preeclampsia. The type A waveform of the pulse wave is recorded in conditions of increased arterial stiffness, as seen in cases of increased endothelial dysfunction. Indeed endothelial dysfunction has been reported in pregnancy-induced hypertension, which has been said to result from defunct nitric oxide metabolism.

This reduces vascular elasticity causing an increased pulse wave velocity and an exaggerated augmentation index [10]. This increased arterial stiffness makes the diastolic pulse wave to return during systole instead of diastole, thus giving the A type of pulse wave on the Complior PWV recording. This is consistent with the findings we report in this paper, where these phenomena were more prominently expressed in the non-dippers and reverse dippers. The exaggerated increase in blood pressure and augmentation index may be responsible for the increased protein loss at the glomerulus. Thus treatment modalities aimed at reducing PWV and dampening the Aix may be better at lowering proteinuria. This is worth further exploration.

Uric acid was significantly associated with the mean arterial pressure in our model. This result is in line with others that have found a positive correlation between uric acid and pulse wave velocity [11]. Uric acid has been said to stimulate the proliferation of vascular smooth muscle cells and oxidative stress and a decrease in the secretion of nitric oxide. Uric acid has also been linked to increased stimulation of the renin-angiotensin-aldosterone pathway [11].

Although sodium concentrations in urine for patients measured in this study were within normal levels with few having lower than average concentrations, significant differences amongst the three groups were recorded with the dippers having the lowest urine sodium concentration. This may be a homeostatic response to retain sodium

concentrations in the vasculature to maintain fetus perfusion [1]. This speculation would have been verified by the measurement of sodium in serum, which was not done in this study. However, this finding is in contrast with others who found no statistical difference in sodium concentration between the dippers and non-dippers [12].

While the creatinine levels were reported to be reasonable in all the participants, there seem to be differences in creatinine handling at the level of nephrons. The non-dippers and reverse dippers had a relatively poor excretory function of creatinine.

This disorder seems to be associated with increased sodium retention in the non-dippers and reverse dippers. The significant correlation also supports the association we found between creatinine and mean arterial pressure.

Increased protein excretion was noted in all the groups, indicating an increase in vascular permeability as being the underlying pathology in all the groups. This may be a result of the toxic substances released from the ischemic placenta, some of which do result in endothelial dysfunction [9, 13, 14].

CONCLUSION

Diurnal variations in hemodynamic parameters were seen in women with preeclampsia, with most having a non-dipping or reverse dipping status, associated with increased cardiovascular risk. The type A waveform recorded in most participants is indicative of endothelial dysfunction in this population, the severity of which is associated with proteinuria. An association between elevated blood pressure readings and proteinuria was seen, indicating a possible causation role in its pathology.

Limitations

A cross-sectional study was employed, and thus, a causal association could not be determined, nor could we determine pregnancy outcomes. Secondly, the sample size is considerably small, calling for caution in the generalization of these results.

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