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THE ASSESSMENT OF ARTERIAL STIFFNESS IN ENDEMIC (BALKAN) NEPHROPATHY PATIENTS UNDERGOING HAEMODIALYSIS

Vedran Premužić[1], Tomislav Teskera[2], Ninoslav Leko[2], Ivana Vuković-Lela[1], Vanja Ivković[1], Mario Laganović[1], Bojan Jelaković[1]

[1] School of Medicine, University of Zagreb, Department of Nephrology, Arterial Hypertension, Dialysis and Transplantation UHC Zagreb, Zagreb, Croatia
[2] Department of Nephrology and Dialysis, Dr Josip Benčević General Hospital, Slavonski Brod, Croatia

Corresponding Author: Vedran Premužić, School of Medicine, University of Zagreb, Department of Nephrology, Arterial Hypertension, Dialysis and Transplantation UHC Zagreb, Zagreb, Croatia; Mob. phone: + 385 91 527 4778, Fax: 385 01 2388 271; E-mail: vpremuzic@gmail.com

Abstract
Cardiovascular (CV) complications are the most important cause of morbidity and mortality in patients with advanced chronic kidney disease (CKD). Arterial stiffness (AS) has been recognized as a strong and independent predictor for CV events in CKD. Our aim was to assess indices of AS in a group of Endemic (Balkan) Nephropathy (EN) patients undergoing haemodialysis (HD). Hypertenison was not considered an importnat feauture in earlier stages of the disease, and therefore we presumed that those patients would have lower AS. Interestingly, we found AS to be even higher in this group of EN patients. This result should be confirmed in a larger cohort of EN patients.

Key words: Endemic (Balkan) Nephropathy, Arterial Stiffness, Haemodialysis, Pulse Wave Velocity, Chronic Kidney Disease.

Introduction

Cardiovascular (CV) complications are the most important cause of morbidity and mortality in patients with advanced chronic kidney disease (CKD), and this was reported even in patients with early stages of renal disease [1]. Besides many other risk factors, arterial stiffness has been recognized as a strong and independent predictor for CV events in CKD [2–6]. Arterial stiffness and its two markers, pulse wave velocity (PWV) and augmentation index (AIx) are strong predictors of CV events especially for patients undergoing hemodialysis (HD) and it was also found in patients with hypertension (AH) and in the general population [7–10]. Clinical features of this toxic nephropathy include severely shrunken kidneys, tubular proteinurija, a positive household history, a slow progression to end-stage renal failure and anaemia [11–15]. There have so far been unconfirmed reports of normal blood pressure (BP), especially in the earlier stages of disease, and therefore lower arterial stiffness in EN patients could be expected. Our aim was to assess AS in our group of EN patients undergoing HD.

Patients and Methods

Subjects

This study was conducted on 82 HD patients (41 m, 41 w) (age: 61.8 ± 13.97 years) from the Dialytic Unit, Slavonski Brod GH. Patients with atrial fibrillation were excluded. There were 29 (12 m, 17 w) EN and 54 (29 m, 24 w) non-EN patients (mean age 61.7 ± 12.0 vs. 68.1 ± 9.5 years, respectively; p = 0.98). Characteristics of the study population are detailed in Table 1. There were 9 patients (4 non-

insulin-dependent diabetes mellitus (NIDDM) and 5 insulin-dependent diabetes mellitus patients (IDDM)) with diabetes mellitus, 10 patients with AH and 2 patients with renovascular hypertension, 39% non-EN patients had a significant risk of CV disease.

Table 1

Characteristics of the EN study group

Number of patients	82
Gender, male/female	41/41
Age, years	61.79 ± 13.97
Height	166.28 ± 10.56
Weight	66.29 ± 13.84
BMI	23.93 ± 3.90
Brachial AIx	13.91 ± 27.20
Aortic AIx	38.46 ± 11.61
Aortic PWV	11.40 ± 2.04
Mean Arterial Pressure	111.85 ± 16.15
Aortic systolic BP	161.87 ± 31.01
Systolic BP	139.89 ± 24.27
Diastolic BP	73.68 ± 12.87
PP	78.27 ± 12.49
Serum RBC count	3.37 ± 0.22
Serum Haemoglobin	110.76 ± 5.68
Serum Haematocrit	0.34 ± 0.03
Serum glucose	5.18 ± 1.66
Serum creatinine	769.39 ± 73.77
Serum K	5.43 ± 0.35
Serum Ca	2.49 ± 0.09
Serum P	2.0 ± 0.19
Serum cholesterol	5.22 ± 0.40
Serum HDL cholesterol	1.45 ± 0.54
Serum LDL cholesterol	2.45 ± 0.54
Serum triglycerides	1.97 ± 0.29
Erythropoietin	3316.45 ± 1354.42

± Values are n or mean;
BMI (body mass index), AIx (augmentation index), PWV (pulse wave velocity), BP (blood pressure), PP (pulse pressure)

Medical history, laboratory parameters and medication data were collected from patients' charts. All patients gave informed consent to participating in this study. The study was approved by the ethical comitees of Slavonski Brod GH and the School of Medicine, University of Zagreb. There were 57 patients (69%) on active vitamin D, 79 patients (96%) on erythropoietin, 17 patients (21%) on Sevelamer and 65 patients (79%) on calcium carbonate therapy. All patients were on folic acid (B9) therapy while none of the patients was on lipid-lowering therapy. Only 25 patients (30%) were on antihypertensive therapy (44% were receiving angiotensin-converting enzyme inhibitors (ACE-I), 0.8% were on calcium-channel blockers (CA-B), 32% were on combined ACE+CA-B therapy and 16% were on combined ACE+other antihypertensives therapy.

Data collection

The following laboratory parameters were collected: cholesterol, HDL, LDL, triglycerides, glucose, creatinine, K, Ca, P, haematocrit, haemoglobin abd RBC count. BMI was calculated as the dry weight divided by the square of body height. The mean value of the three measurements of the postdialytic body weight was defined as dry weight. All measurements were performed before the dialysis session in a calm environment with the patient in a resting position for at least fifteen minutes. Brachial BP was measured using an Omron device (HEM-780-D; Omron, Kyoto, Japan) in a seated position and was determined as the mean of three measurements on the nonfistula arm. Mean arterial pressure (MAP) was calculated as DBP + ((SBP-DBP)/3) and pulse pressure was calculated as SBP-DBP. We assessed arterial stiffness and its two markers PWV and AIx by the Tensiomed Arteriograph device (Medexpert Ltd., Budapest, Hungary). After assessing the length of the aorta by approximation jugulum-symphysis we conducted the measurement which gave us the following parameters: systolic BP, diastolic BP, heart rate (HR), mean arterial pressure (MAP), pulse pressure (PP), brachial AIx, aortic AIx, aortic PWV and aortic systolic BP.

Statistical analysis was performed using WinStat ver. 4.0 Statsoft Inc. The Nnrmality of data distribution was tested using the Kolmogorov-Smirnov test. With the aim of describing the distribution of continuous variables, means and SDs were used. Differences in means established between the groups were tested using the Student t-test or Mann-Whitney U test, while the x2-test was used for the purpose of inter-group prevalence comparisons.

Results

There were no differences in gender, body mass index, brachial BP, serum creatinine, electrolytes, lipids and drug therapy (including erythropoietin) between the EN and non-EN groups. However, RBC count, haemo-

globin and haematocrit were significantly lower in the EN group (3.29 ± 0.2 vs. 3.42 ± 0.22; p = 0.0087; 108.58 ± 4.35 vs. 111.94 ± 5.99; p = 0.009; 0.33 ± 0.02 vs. 0.35 ± 0.03; p = 0.003). Brachial and aortic AIx were significantly higher in EN patients (24.8 ± 26.6 vs. 7.2 ± 25.8; p = 0.005; 43.1 ± 11.3 vs. 35.6 ± 10.9; p = 0.005, respectively) as well as aortic PWV (12.1 ± 2.0 vs. 10.9 ± 1.9; p = 0.01) (Table 2).

Table 2

Differences between EN and non-EN patients

	EN group	Non-EN group	p
Number of patients	29	53	
Age, years	61.76 ± 12.33	61.81 ± 14.91	0.98
Height	163.58 ± 12.06	167.66 ± 9.54	0.09
Brachial AIx	24.86 ± 26.65	7.27 ± 25.88	0.005
Aortic AIx	43.11 ± 11.30	35.65 ± 10.97	0.005
Aortic PWV	12.14 ± 2.05	10.95 ± 1.92	0.012
Mean Arterial Pressure	112.37 ± 16.33	111.77 ± 16.28	0.87
Aortic systolic BP	165.43 ± 30.03	159.73 ± 31.71	0.44
Systolic BP	135.01 ± 23.99	142.56 ± 24.23	0.18
Diastolic BP	71.85 ± 12.98	74.68 ± 12.82	0.34
PP	78.14 ± 12.07	78.36 ± 12.82	0.93
Serum RBC count	3.29 ± 0.20	3.42 ± 0.22	0.008
Serum Haemoglobin	108.58 ± 4.35	111.94 ± 5.99	0.009
Serum Haematocrit	0.33 ± 0.02	0.35 ± 0.03	0.003
Serum glucose	4.69 ± 0.37	5.45 ± 2.01	0.04
Serum creatinine	765.52 ± 58.62	771.51 ± 81.33	0.73
Serum K	5.37 ± 0.37	5.46 ± 0.34	0.25
Serum Ca	2.48 ± 0.08	2.50 ± 0.09	0.53
Serum P	1.92 ± 0.20	2.04 ± 0.17	0.005
Serum cholesterol	5.17 ± 0.39	5.25 ± 0.41	0.43
Serum HDL cholesterol	1.48 ± 0.67	1.43 ± 0.46	0.68
Serum LDL cholesterol	2.42 ± 0.43	2.47 ± 0.59	0.64
Serum triglycerides	1.84 ± 0.29	2.04 ± 0.26	0.002
Erythropoietin	3142.87 ± 1380.13	3411.76 ± 1344.27	0.4

Values are n or mean ±
BMI (body mass index), AIx (augmentation index), PWV (pulse wave velocity), BP (blood pressure), PP (pulse pressure), EN (endemic nephropathy)

In EN patients, we found a significantly positive correlation between RBC count, serum haemoglobin concentration, haematocrit, and brachial and aortic AIx (r = 0.54; 0.50, 0.38, respectively; p < 0.05). In the non-EN group, we failed to find these associations. Moreover, in EN patients aortic PWV was not associated with anaemia, while in the non-EN group it was significantly but inversely correlated (r = -0.34; p < 0.05). In both EN and non-EN patients, aortic PWV was significantly correlated with central systolic BP (r = 0.74, 0.67, respectively; p < 0.05).

Discussion

In this study we used the Arteriograph Tensio Med Clinic device for the assessment of arterial stiffness and its two markers PWV and AIx. It was validated in different studies. vs. other non-invasive automatic devices [16–18]. Arteriograph is a device which by an oscillometric method detects pulsatile pressure changes in the brachial artery. It measures BP, PWV and AIx simultaneosly. As we know, arterial stiffness is now defined as an important CV risk predictor in hypertension and ESRD as well and it is also recomended in current ESH/ESC guidelines [19, 20]. There are different parameters by which we can determine arterial stiffness markers values. Ventricular ejection and vascular resistance to flow in the aorta and central arteries determines the PWV, which is correlated with body height. The differences in PWV values between taller and

smaller patients have been explained by the early return of the reflected wave caused by the shorter body length which is partly compensated for by the higher heart rate in short people [21, 22]. Use of different antihypertensive drugs has different influences on arterial stiffness. There are several trials which have indicated a positive influence of ACE inhibitors on arterial stiffness [23]. Unfortunately we have failed to find any significant differences between patients on antihypertensive therapy and without therapy, but nevertheless the impact of some drugs (ACE-I, ARB and statins) on arterial stiffness is important for clinical practice [24–26]. Our results showed that brachial and aortic AIx were higher in EN patients as well as aortic PWV. Severely shrunken kidneys, slowly progressing tubulointerstitial chronic nephritis, progression to end-stage renal failure and severe normo- or hypochromic normocytic hyporegenerative anaemia leads to higher values of PWV and AIx in EN patients. Renal cortex deterioration decreases erythropoietin secretion and as a result there is lower RBC count, haemoglobin and haematocrit values [13, 15]. Our results are in favour of these clinical findings (a significantly positive correlation between RBC count, serum haemoglobin concentration, haemoglobin and brachial and aortic AIx). Comparing our results with Schwarz et al. [27] we observed an inverse relationship between aortic PWV and anaemia, while we did not find these associations in the EN group of patients. The second arterial stiffness marker, Aix, was significantly correlated with anaemia in EN patients. These results were similar to Covic et al. [28]. The importance of anaemia treatment in ESRD and especially in EN patients is once more confirmed by these results.

There are some limitations to our study. First, the follow-up of these patients is missing. With continuance in observation of the patients, their therapy and disease progression, it would be easier to estimate their risk factors and CV outcome just evaluating arterial stiffness marker values as well as the other parameters. Second, the design of our study is a cross-sectional one, and therefore makes it difficult to analyse the trends of arterial stiffness characteristics over time. These are only preliminary data gathered from a small group of patients, especially EN patients.

In conclusion, arterial stiffness is increased in patients with EN undergoing dialysis and is higher than the arterial stiffness observed in the non-EN group. Differences in the association of arterial stiffness with anaemia were observed between EN and non-EN patients. Further studies are needed to explain these results.

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Резиме

ПРОЦЕНА НА АРТЕРИСКА ВКОЧАНЕТОСТ КАЈ ПАЦИЕНТИ СО ЕНДЕМСКА (БАЛКАНСКА) НЕФРОПАТИЈА НА ХЕМОДИЈАЛИЗА

Ведран Премужиќ[1], Томислав Тескера[2], Нинослав Леко[2], Ивана Вуковиќ-Лела[1], Вања Ивковиќ[1], Марио Лагановиќ[1], Бојан Јелаковиќ[1]

1 Медицински факултет, Универзитет во Загреб, Оддел за артериска хипертензија, дијализа и трансплантација, УХЦ Загреб, Загреб, Хрватска
2 Оддел за нефрологија и дијализа, Општа болница „Д-р Јосип Бенчевиќ“, Славонски Брод, Хрватска

Кардиоваскуларните (КВ) компликации се најважната причина за морбидитет и морталитет кај пациентите со напредна хронична бубрежна болест (ХББ). Артериската вкочанетост (АС) е призната како силен и независен предвидувач за КВ настаните во ХББ. Нашата цел беше да се оценат индексите на АС кај група пациенти со ендемска (балканска) нефропатијата (ЕН) што се на хемодијализа (ХД). Хипертензијата не се сметаше за важна карактеристика во претходните фази на болеста и затоа претпоставивме дека тие пациенти ќе имаат пониски АС. Интересно, откривме дека АС се дури и поголеми кај групата пациенти со ЕН. Овој резултат треба да се потврди во поголема група пациенти со ЕН.

Клучни зборови: ендемска (балканска) нефропатија, артериска вкочанетост, хемодијализа, брзина на пулсирачки бран, хронична бубрежна болест.