Neutrophil-to-lymphocyte ratio and pulse wave velocity in patients with controlled systemic hypertension — a preliminary report

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Abstract

Background. Increased arterial stiffness assessed by pulse wave velocity (PWV) measurement is a marker of arterial wall dysfunction and has an independent predictive value for adverse cardiovascular outcomes. A positive correlation between the neutrophil-to-lymphocyte ratio (NLR) and PWV has been reported in chronic inflammatory conditions and the general population as well.

Furthermore, an association between NLR and PWV has been assumed in hypertensive patients. However, the available data are scarce.

The objective of the study was to validate the association between NLR and PWV in a homogenous group of controlled-hypertensive patients without chronic inflammatory conditions.

Material and methods. A retrospective observational study was conducted in outpatient cardiology and a general practice. A total number of 25 already on-target treated essential hypertensive, non-diabetic and non-chronic kidney disease (non-CKD) patients were selected. PWV was automatically calculated for each patient using the ABPM BPLab® device. The following laboratory data were collected: complete blood count, fibrinogen, alkaline phosphatase, lactate dehydrogenase, uric acid, serum glucose, total cholesterol, triglycerides, iron, calcium, and creatinine. Neutrophil-to-lymphocyte ratio was calculated. Antihypertensive treatment classes were also assessed.

Results. A correlation between increased NLR and PWV in a homogenous group of controlled-hypertensive patients was identified.

Conclusions. There is an evident relation between increased NLR and increased PWV in controlled hypertensive patients without evidence of chronic inflammatory conditions.

Key words: neutrophil-to-lymphocyte ratio; pulse wave velocity; hypertension

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Introduction

The leading cause of morbidity and mortality worldwide is represented by cardiovascular diseases (CVD); hypertension is considered a major risk factor for heart disease, being ranked the third most common cause leading to disability in the world [1].

Arterial stiffness is characterized by degeneration of extracellular matrix in the media layer of elastic arteries with loss of elastic fibres, and increased fibrosis as a consequence of increased cyclic stress [2]. The changes in arterial stiffening are morphologically different from atherosclerosis, a process that involves the intima layer and is characterized by patchy intimal thickening with subsequent lumen narrowing [3].

Increased arterial stiffness is considered to be the initial indicator of arterial wall dysfunction and has an independent predictive value for adverse CV outcomes, along with traditional CV risk factors [4–6]. Patients with diabetes mellitus, metabolic syndrome, or chronic inflammation status are at high risk of developing increased arterial stiffness [7, 8].

Pulse wave velocity (PWV) is the most commonly used method for arterial stiffness assessment [9].

As arterial stiffening affects mainly the proximal arteries, the stiffness gradient between proximal and distal arteries will subside leading to decreased wave reflection from the resistance vessels, and consequently increased pressure in the microcirculation, with negative effects on the perfused organs, particularly brain and kidney [10].

Additionally, a reduced arterial filling capacity as a consequence of increased stiffness leads to an enhanced pulse pressure (PP) and causes prematurely recoil of the reflected waves with a consequent enhancement of late systolic pressure and gradual left ventricular hypertrophy development [11, 12].

Although PWV is indisputably an excellent tool for CV risk stratification, it also bears relevant limitations [13]. Pulse wave velocity is influenced by many clinical factors like age, blood pressure (BP) and other traditional CV risk factors [14]. For proper evaluation, target BP control should be achieved before PWV determination [9].

As a result of the age-related reduction in nitric oxide synthesis and increased vasoconstrictor availability, elder individuals present impairment in vascular function leading to decreased resistance to oxidative stress and changes in vascular structure with wall thickening and increased stiffness in conduit arteries [15–17]. Consequently, the function of preserving a constant BP against a pulsating blood flow is more impaired in elderly individuals.

For PWV assessment, invasive and non-invasive methods are accessible, non-invasive methods being currently available in clinical practice. Arterial stiffness can be determined by non-invasive carotid-femoral PWV computation using a tonometry device [14, 15].

Pulse wave velocity cut-off values vary among different populations as a consequence of the many confounders. In middle-aged patients with hypertension, a PWV value higher than 10m/s is associated with significant aortic function deterioration [15, 18].

Ambulatory 24-hour PWV analysis is a validated arterial stiffness measurement that also involves assessment of central arterial pressure (CAP) and augmentation index (AIx) calculations, both being able to be estimated from the common carotid artery or a peripheral artery (i.e. brachial artery) waveform [19–21].

The neutrophil-to-lymphocyte ratio (NLR) is currently investigated as an inflammatory marker. NLR is associated with atherosclerosis, hypertension, coronary artery disease, acute coronary syndromes and other known inflammatory conditions; additionally, NLR may be an indicator of disease severity of coronary artery disease and calcific atherosclerosis [23–27].

A positive correlation between NLR and PWV in the general population has been reported in previous studies, but also in research focused on chronic inflammatory conditions [28–30]. Furthermore, an association between PWV and NLR in hypertensive patients identified NLR as a valid index for arterial stiffness [31]. Nevertheless, a relationship between NLR and arteriosclerosis in hypertensive patients is scarce.

The premise of our study was to validate the association between NLR and arterial stiffness assessed by PWV in a homogenous group of controlled-hypertensive patients.

Material and methods

A retrospective observational study was conducted in outpatient cardiology and a general practice. Data were collected after the study protocol approval by local Ethics Committee no. 1172/14/01/2019. All the subjects afforded written informed consent.

A total number of fifty-nine unselected, already treated at target essential hypertensive adult patients underwent a 24-hour ambulatory blood pressure monitoring (ABPM) evaluation from June 2016 to June 2017, using a BPLab® device (BPLab® GmbH, Schwalbach am Taunus, Germany); derived used parameters were: mean arterial pressure (MAP) and pulse wave velocity (PWV).

Subjects with any of the following concomitant diagnosis: atrial fibrillation, frequent ectopic beats, secondary hypertension, documented or suspected cardiomyopathy, chronic inflammatory conditions, infectious diseases, or malignant tumours were excluded from statistical analysis. In addition, we did not include in our research patients with antihypertensive regimens containing amlodipine or valsartan. Patients were instructed to avoid alcohol, caffeine-containing products and substantial meal 8 hours before and during 24-hour monitoring.

The 24-hour BP reports along with the laboratory tests performed within the monitoring time frame, anthropometric and demographic data were retrospectively collected from an integrated electronic database.

The carotid-femoral PWV was automatically calculated using the ABPM BPLab® device, which is an automatic, validated device to measure the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid and the femoral arteries, over a 24 hours period [32]. The "surrogate" length of the aorta was measured non-invasively with a non-elastic tape measure, between carotid and femoral artery. In order to reduce variations in the measurements, one trained technician performed PWV data collection.

With respect to the inclusion and exclusion criteria, a total number of 25 already treated at target essential hypertensive, non-diabetic and non-CKD patients were included in the study. Out of these patients, seventeen were males (68.0%) and eight were females (32.0%).

The following laboratory data were collected: complete blood count, fibrinogen, alkaline phosphatase, lactate dehydrogenase, uric acid, serum glucose, total cholesterol, triglycerides, iron, calcium, and creatinine. Neutrophil-to-lymphocyte ratio was calculated. Glomerular filtration rate was estimated using the CKD-EPI formula. Antihypertensive treatment classes were also assessed.

The association between the qualitative variables was assessed using the Student's t-test. P values < 0.05 were considered statistically significant, and all confidence intervals are 95%. Linear regression analysis was performed in order to test the relationship between selected parameters, Pearson product-moment correlation coefficient (r) was used to assess the strength of the association. The statistical analysis was performed using SPSS 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, USA), and Graph Pad Prism 8.1.2 (227) software (GraphPad Software Inc., San Diego, USA).

Results

The mean age of our study group (25 patients) was 54.96 ± 13.03 (range 29–87) years old; mean age in the male subgroup was 53.45 ± 14.59 years old and mean age in the female subgroup was 55.68 ± 14.6 years old, respectively. Subject's body mass index (BMI) was 29.77 ± 4.10 kg/m^2 (range 20.50–35.50 kg). Overweight was diagnosed in 45% of the study subjects, 45% have obesity grade I and 5% obesity grade II. Distinctive laboratory descriptive data and their correlation to PWV are depicted in Table 1.

Table 1. Laboratory descriptive data and their correlation to pulse wave velocity (PWV)

Parameters	N	Min	Max	Range	PWV	
					p value	Pearson's r
Neutrophils (NV: 1.5–7.5 × 10^3/μL)	25	2.46	8.45	5.99	–	
Lymphocytes (NV: 1.0–4.0 × 10^3/μL)	25	0.82	4.00	3.18	–	
NLR	25	9.10	15.70	6.60	–	
Fibrinogen (NV: 1.5–4.0 g/L)	12	2.40	5.50	3.10	0.04	0.58
Alkaline phosphatase (NV: 100–300 U/L)	21	57.00	352.00	295.00	0.32	0.22
Lactate dehydrogenase (NV: 240–480 U/L)	18	149.00	440.00	291.00	0.97	–0.01
Uric acid (NV: 200–400 U/L)	23	173.30	749.00	575.70	0.11	0.33
Serum glucose (NV: 4–5.4 mmol/L)	25	4.41	9.99	5.58	0.01	0.57
Total cholesterol (NV: 2.8–5.2 mmol/L)	25	3.15	8.48	5.33	0.97	0.01
Triglyceride (NV: 0.55–1.90 mmol/L)	22	0.61	10.60	9.99	0.41	0.03
Iron (NV: 9.0–30.4 μmol/L)	15	9.20	23.30	14.10	0.63	0.13
Total calcium (NV: 2.15–2.57 mmol/L)	16	1.94	2.53	0.59	0.75	0.08

N — number of patients; Min — minimum; Max — maximum; NV — normal values; NLR — neutrophil-to-lymphocyte ratio

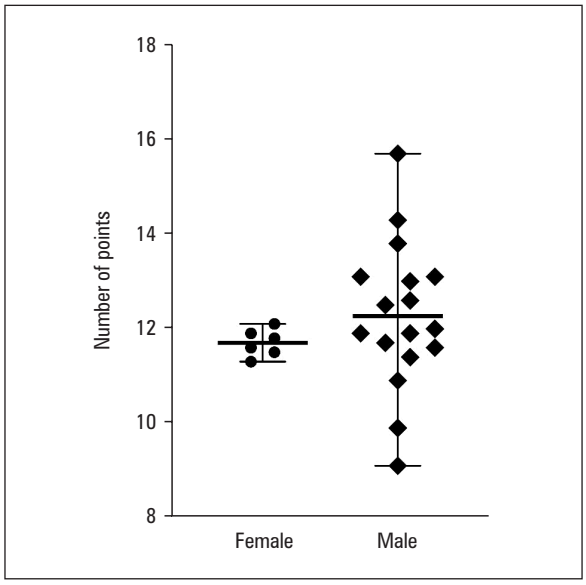

Figure 1. Pulse wave velocity (PWV) values by gender distribution

Results outlined in Table 1 demonstrates a positive correlation between fibrinogen and PWV (p = 0.04, Pearson's *r* = 0.58) and between serum glucose and PWV (p = 0.01, Pearson's *r* = 0.57).

Pulse wave velocity (m/s) was analysed by gender distribution as presented in Figure 1; within the two subgroups, no statistically significant difference was identified (p = 0.46).

Age and ABPM BPLab® derived data (MAP, PWV) correlated to neutrophil-to-lymphocyte ratio were analysed, as presented in Table 2.

A correlation between PWV and NLR (p < 0.01) was found in our statistical analysis. We could not identify a statistically significant correlation between NLR and MAP, although there is a positive correlation (p = 0.48) (see Tab. 2).

In the interest of analysing the impact of disease duration and age-dependent NLR on PWV, the study population was divided according to age (≥ 50 years and ≥ 60 years). Analysis of Pearson's correlation test regarding the association between age and age-dependent NLR to PWV is presented in Table 3.

Regarding age-dependent NLR, for subjects in age groups 50 years and older, we identified a correlation between NLR and PWV as is illustrated in Table 3 (p = 0.01, Pearson's *r* = 0.71). For subjects in the age group 60 years and older, we identified a correlation between NLR and PWV as seen in Table 3 (p = 0.01, Pearson's *r* = 0.85).

Table 2. Neutrophil-to-lymphocyte (NLR) ratio correlation to 24-hour ambulatory blood pressure monitoring (ABPM) derived data, and age in the studied group

Parameters		NLR	MAP	PWV	Age
NLR	Pearson's *r*	1	0.15	0.65	0.37
	p value	–	0.48	0.00	0.07
MAP	Pearson's *r*	0.15	1	0.51	–0.02
	p value	0.48	–	0.01	0.94
PWV	Pearson's *r*	0.65	0.51	1	0.36
	p value	0.00	0.01	–	0.08
Age	Pearson's *r*	0.37	–0.02	0.36	1
	p value	0.07	0.94	0.08	–

MAP — mean arterial pressure; PWV — pulse wave velocity

Table 3. Pulse wave velocity (PWV) correlation to age and neutrophil-to-lymphocyte (NLR) in studied subjects

Parameters	PWV			
	p	95% CI	Pearson's *r*	N
Age ≥ 50	0.09	–0.07 to 0.73	–0.40	18
Age ≥ 60	0.55	–0.51 to 0.77	0.22	9
NLR for age ≥ 50	0.01	0.36 to 0.88	0.71	18
NLR for age ≥ 60	0.01	0.45 to 0.96	0.85	9

CI — confidence interval; N — number of patients

Discussions

The neutrophil-to-lymphocyte ratio is a simple, readily available, inexpensive marker of inflammation and is expected to be a marker of oxidative stress as well. A relation between NLR and hypertension has been reported in previous studies, as increased NLR in elderly hypertensive patients was associated with increased all-cause mortality [33]. Moreover, NLR was raised in prevalent hypertensive patients and also in individuals with incident hypertension [34, 35].

Even though NLR is a reliable marker of inflammation, it should be considered that NLR levels may be influenced by different situations such as hydration fluctuation [36]. Furthermore, when interpreting different study results concerning NLR values, antihypertensive drugs should be considered, as amlodipine and valsartan administration may decrease NLR [24]. Because use of valsartan reduced interleukin 6 and tumour necrosis factor α in hypertensive patients in previous studies and valsartan and amlodipine as well were reported to decrease oxidative stress and inflammatory response [24], we believe that patients benefiting from these antihypertensive regimens will experience reduced NLR values in comparison with patients treated with other antihypertensive regiments, thus preventing us from properly assessing the correlation between NLR and PWV.

Neutrophil-to-lymphocyte ratio is also an accurate marker for the atherosclerotic disease, which might be related to the influence of the autonomic nervous system as lymphocytes present cholinergic receptors while granulocytes expose adrenergic receptors. Sympathetic nervous system stimulation can increase granulocytes number, and parasympathetic nervous system stimulation can increase lymphocytes [37]. Consequently, vessel sympathetic overactivation, which is encountered in hypertension, heart failure, acute coronary syndromes and arrhythmias, can lead to increased neutrophils and endothelial dysfunction, an essential step in atherosclerotic plaque development [38]. Furthermore, central and peripheral artery stiffness are reported as enhanced under the influence of increased muscle sympathetic nerve activity, which leads to the reasonable assumption that sympathetic hyperactivity might be a contributing factor to the association between increased NLR and PWV [39].

The correlation between NLR and arterial stiffness has been reported in multiple previous studies, particularly in individuals diagnosed with chronic inflammatory conditions. Statistically significant associations were found in patients with systemic lupus erythematosus, a pathology long known to bare important traditional and non-traditional CV risk factors, and also in patients with inflammatory bowel disease, a pathology with a low prevalence of traditional CV risk factors [30, 40].

There are few studies investigating a relation between NLR and PWV that included individuals without a significant inflammatory condition. Additionally, records aiming to identify an association between PWV and NLR in hypertensive patients are limited as well. Nevertheless, there are data describing NLR as a valid indicator for arterial stiffness in hypertensive patients [41].

Our study identified a statistically significant association between NLR and arterial stiffness assessed by PWV analysis in a homogenous group of hypertensive patients. Furthermore, we identified a positive correlation between fibrinogen and PWV as well. Even though a relation between NLR and arterial stiffness in hypertensive patients has been reported before, the novelty of our study consists in the homogenous population included, with controlled hypertension and lacking in confounding factors for NLR. Patients with confounding factors for PWV such as atrial fibrillation, frequent ectopic beats, secondary hypertension, documented or suspected cardiomyopathy were excluded in order to assess a relationship between PWV and NLR accurately. For the same purpose, patients with inflammatory conditions (diabetes, CKD, infectious diseases, malignant tumours, other chronic inflammatory conditions) already known to present increased NLR and a high risk for increased PWV were also excluded.

In patients aged 60 and older, hypertension is the most frequent cardiovascular condition. For proper evaluation of the influence on PWV of disease-duration-dependent hypertension, we further divided our study group according to age as follows: patients ≥ 50 years and patients ≥ 60 years. Ageing, which we assume is associated with prolonged hypertensive disease duration, did not have a statistically significant correlation to PWV, most likely due to the small sample group. As expected, aged-dependent NLR was associated with PWV in each age group.

Impaired glucose tolerance stimulates non-enzymatic glycation and cross-linking of collagen, thus contributing to increased arterial stiffness [42]. Glucose serum levels also proved to be correlated to PWV in our study population. We included non-diabetic patients, with incidental low-level hyperglycaemia recorded in a small number of individuals; hence we believe the positive correlation between glycaemia and PWV may be casual in our subjects, mainly as a result of small sample size.

Our research has several inherent limitations. First, our study was a retrospective observational one which included a cluster of patients from the urban area, highly adherent to antihypertensive treatment, which may have different characteristics from the general hypertensive population. We did not include confounding factors (i.e. regional anthropometric indices) that could influence our results. Second, PWV was not determined prior to BP optimal control. In addition, the sample size of our research work was limited due to recent relative availability to use the BPLab® device, which may contribute to the results.

Conclusion

There is an evident relation between increased neutrophil-to-lymphocyte ratio and increased pulse wave velocity in controlled hypertensive patients with no confirmation of chronic inflammatory conditions. Further directed investigations are required through prospective studies.

Author contributions

Conceptualization: A.V., C.F.S., and C.F.B.; methods: A.V., C.F.S., D.N.P, and C.F.B.; statistical analysis: A.V., T.Z., and C.F.B.; validation: A.V., T.Z., C.F.S., D.N.P, and C.F.B; investigation: A.V., T.Z., C.F.S., and D.N.P.; resources: A.V., C.F.S., and D.N.P.; data curation: A.V., C.F.S., C.F.B.; writing — original draft preparation: A.V., T.Z., C.F.S., D.N.P., and C.F.B.; writing — review and editing: A.V., T.Z., C.F.S., D.N.P, and C.F.B.; figures: A.V., T.Z., C.F.S., D.N.P., and C.F.B.; supervision: A.V., C.F.S., and C.F.B.; project administration: A.V., and C.F.B. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare no potential conflict of interest regarding this paper.

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