

# The “Pulse Time Index of Norm” highly correlates with the left ventricular mass index in patients with arterial hypertension

Igor N Posokhov<sup>1</sup>  
Natalya N Kulikova<sup>2</sup>  
Irina V Starchenkova<sup>2</sup>  
Elena A Grigoricheva<sup>3</sup>  
Vitaly V Evdokimov<sup>3</sup>  
Artemy V Orlov<sup>4</sup>  
Anatoly N Rogoza<sup>5</sup>

On behalf of The BPLab-  
Vasotens Registry  
Collaborators

<sup>1</sup>Hemodynamic Laboratory Ltd, Nizhny Novgorod, Russia; <sup>2</sup>3rd Republican Hospital, Saransk, Russia; <sup>3</sup>Chelyabinsk State Medical Academy, Chelyabinsk, Russia; <sup>4</sup>National Research Nuclear University MEPhI, Moscow, Russia; <sup>5</sup>Cardiology Research Center, Moscow, Russia

Correspondence: Igor N Posokhov  
PO Box 69, Hemodynamic Laboratory  
603009, Nizhny Novgorod, Russia  
Tel +7 915 939 6222  
Fax +7 913 825 9111  
Email [posokhov@24h-monitoring.com](mailto:posokhov@24h-monitoring.com)

**Background:** Arterial stiffness, as measured by the pulse wave velocity (PWV), is recommended for routine use in clinical practice as an important parameter for the evaluation of cardiovascular risk.<sup>1</sup> New 24-hour monitors (eg, with Vasotens<sup>®</sup> technology; Petr Telegin Company, Nizhny Novgorod, Russian Federation) provide single PWV measurements as well as several PWV measurements over a period of 24 hours.<sup>2</sup> Such 24-hour pulse wave analysis led to the development of the novel Pulse Time Index of Norm (PTIN), which is defined as the percentage of a 24-hour period during which the PWV does not exceed the 10 m/second PWV threshold. The aim of this study is to test the new PTIN for correlation with the left ventricular mass index (LVMI).

**Methods:** Oscillometrically generated waveform files (n=137) used for clinical research studies were reanalyzed using the new 2013 version of the Vasotens technology program, which enables PTIN calculations.

**Results:** A good correlation ( $r=-0.72$ ) between the PTIN and the LVMI was shown, which was significantly above the blood pressure load ( $r=0.41$ ).

**Conclusion:** The PTIN generated by the Vasotens technology can be recommended as an indicator of end organ damage via hypertension.

**Keywords:** pulse wave velocity, ambulatory, 24-hour, monitoring, PTIN, arterial stiffness, LVMI

## Introduction

Arterial stiffness, as measured by the pulse wave velocity (PWV), is recommended for routine use in clinical practice as an important “vascular” index for the evaluation of cardiovascular risk.<sup>1</sup> The PWV relates the capability of an artery to expand and contract under the influence of blood pressure (BP) changes. The PWV and other stiffness indices are independent predictors of cardiovascular morbidity and mortality in hypertensive patients, in elderly populations, in patients with end-stage renal disease, and in patients with type 2 diabetes.<sup>1</sup>

A novel cuff-based method, such as Vasotens<sup>®</sup> (Petr Telegin Company, Nizhny Novgorod, Russian Federation), determines the PWV from oscillometric measurements of the brachial artery waveform. This system for PWV measurements integrated into an ambulatory BP monitoring (ABPM) system provides single PWV measurements as well as several PWV measurements over a period of 24 hours. Such 24-hour pulse wave analysis has led to the development of the novel Pulse Time Index of Norm (PTIN), which is defined as the percentage of a 24-hour period during which the PWV does not exceed the threshold of the PWV of 10 m/second.<sup>2,3</sup>

This cutoff value is well known as a threshold for hypertensive target organ damage.<sup>1,4,5</sup> The PTIN calculation is similar to the principle of the BP load calculation. Several studies have shown that the mean 24-hour BP did not correlate with the left ventricular mass index (LVMI); however, an increased BP load was associated with a higher LVMI.<sup>6,7</sup>

Does the PTIN provide additional information about cardiovascular risk? Recently registries have been established in European countries to assess the impact of ABPM on hypertension management and related outcomes. ABPM registries are more commonly focused on patients with documented or possible hypertension who would benefit from ABPM. The BPLab-Vasotens registry that was established this year is the project of dozens of small groups aimed at joint solutions for various scientific problems. One of the challenges is research into new ABPM “vascular” indices.

To study the association of the PTIN with the LVMI, we used the ability to work with archives of the BPLab-Vasotens registry, which is provided by a unique feature of the Vasotens technology. This technology processes the oscillometrically generated waveform files that are received, digitized, and stored into the computer memory by the BPLab® (Petr Telegin Company) software for ABPM. The data processing can be performed during the analysis or at any time after the ABPM study.

## Methods

### Baseline characteristics

Overall, 137 oscillometrically generated waveform files that had previously been used in clinical research studies with ABPM were reanalyzed using the new 2013 version of the Vasotens technology program. The detailed baseline characteristics of the patients whose waveform files were used are shown in Table 1. These were patients with arterial hypertension; athletes and patients with a body mass index greater than 27.5 kg/m<sup>2</sup> were excluded from the study.

All of the studies in which the data were reanalyzed were authorized by the local ethics commissions. All of the enrolled patients provided written informed consent.

### Vasotens

The Vasotens technology is an innovative method for pulse wave analysis based on oscillometric BP measurement by the BPLab device (Petr Telegin Company).<sup>8,9</sup> The method of PTIN calculation consists of assessing the PWV. The PWV estimation method used for this parameter is based on identification of the reflected wave on the pulse curve at the arteria brachialis, taking into account the delay of the

**Table 1** The baseline characteristics of the examined patients, n=137

Characteristic	Value
Male, n (%)	83 (61)
Age, mean (SD) years	46 (18)
Height, mean (SD) cm	168 (7)
Weight, mean (SD) kg	83 (17)
SBP, mean (SD) mmHg	144 (23)
DBP, mean (SD) mmHg	82 (13)
Heart rate, mean (SD) bpm	73 (14)
Hypertension, n (%)	137 (100)
Duration of hypertension history, mean (SD) years	6 (3)
Medication: thiazide diuretics, n (%)	80 (58)
Medication: angiotensin-receptor blockers, n (%)	91 (66)
Medication: beta-blockers, n (%)	60 (44)
Medication: other, n (%)	51 (37)
Drug combinations, n (%)	128 (93)
Previous MI or stroke, n (%)	26 (19)
LVH, n (%)	75 (55)
Renal disease, n (%)	4 (3)

**Abbreviations:** DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; MI, myocardial infarction; SBP, systolic blood pressure; SD, standard deviation.

reflected wave relative to the direct wave. The transit time of both the direct wave and the reflected wave is equal to double the length of the aortic trunk. A more detailed description of the method was published in a recent review.<sup>2</sup>

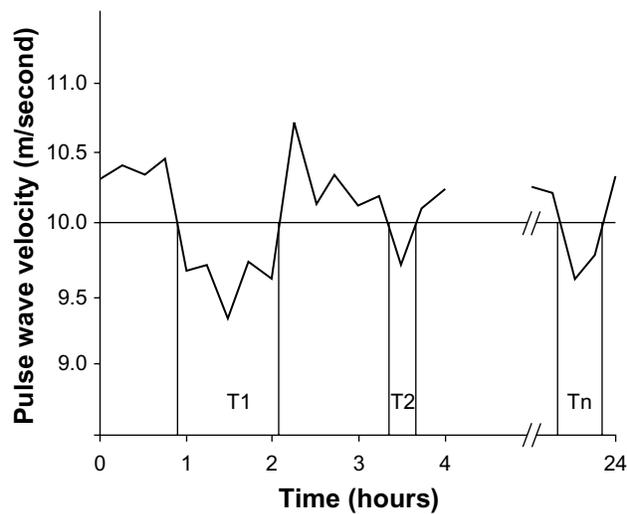
Recordings are made in the ambulatory (ie, 24-hour) measurement mode using a conventional BP cuff for adults. During the BP measurement, the pressure waveforms in the cuff are registered while performing a step-by-step deflation. The separation and timing of the forward and reflected pulse waves are performed by a Vasotens mathematical algorithm. The distance for the PWV equation used in this technology was measured in accordance with the manufacturer's instructions. Quality control is based on visual assessment of the curves in the Vasotens clinical report screen. The PTIN calculation is illustrated in Figure 1.

### BP load

We found it appropriate to use the identical BPLab device to evaluate the BP load because the hardware has an A/A class of accuracy for BP measurement.<sup>10</sup> The BP load is defined as the percentage of a 24-hour period in which either the systolic BP exceeds the cutoff values of 135 mmHg during the day and 120 mmHg at night or the diastolic BP exceeds the cutoff values of 85 mmHg during the day and 70 mmHg during the night.

### LVMI

The LVMI was determined for 137 hypertensive patients using two-dimensional guided M-mode echocardiography performed



**Figure 1** The PTIN calculation principle.

**Notes:** T1, T2 and Tn are the periods in which the PWV does not exceed the cutoff value of 10 m/second.  $PTIN, \% = (T1 + T2 + \dots + Tn) / Tm \times 100$ , where Tm is the entire period of monitoring, Pulse Time Index of Norm.<sup>2,22</sup>

**Abbreviations:** PTIN, Pulse Time Index of Norm; PWV, pulse wave velocity.

with standard methods using an ultrasound system (Logiq 9 and Logiq 7 Ultrasound Machine; General Electric, Fairfield, CT, USA) with a 2.25-MHz transducer. The left ventricular internal dimension (LVID), the interventricular septal thickness (IVST), and the posterior wall thickness (PWT) were measured during the end diastole period, in accordance with the American Society of Echocardiography (ASE) recommendations.<sup>11</sup> The left ventricular (LV) systolic and diastolic diameters and the IVST and the PWT were measured during the end diastole period, which was defined by the beginning of the qRS-complex. The left ventricular mass (LVM) was calculated using the following corrected ASE formula by Devereux et al:<sup>12</sup>

$$LVM = 1.04 \times \{ [LVID + PWT + IVST]^3 - LVID^3 \} \times 0.8 + 0.6, \quad (1)$$

where LVID, left ventricular PWT, and IVST are measured in centimeters. The LVM was indexed by the body surface area (LVM/BSA, g/m<sup>2</sup>), which was calculated using the Dubois formula, and by height<sup>2.7</sup> (LVM/height<sup>2.7</sup>, g/m<sup>2.7</sup>), as recommended by de Simone et al.<sup>13</sup> We set the cutoff values for left ventricular hypertrophy (LVH) as LVM/BSA  $\geq 116$  g/m<sup>2</sup> in males and  $\geq 96$  g/m<sup>2</sup> in females; the cutoff value for the LVM/height<sup>2.7</sup> was  $\geq 49$  g/m<sup>2.7</sup> in males and  $\geq 45$  g/m<sup>2.7</sup> in females.<sup>14</sup>

## Statistics

We used BPStat (Petr Telegin Company) software, version 05.00.04 for the automatic tabulation of the indices of every

measured waveform. Statistica (StatSoft Inc., Tulsa, OK, USA) software for Windows 8.0 was used for the analysis.

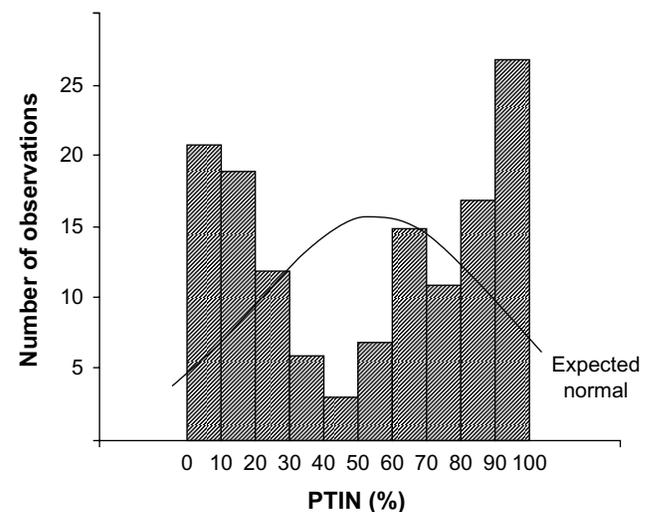
## Results

The 137 hypertensive patient ABPM waveform files were reanalyzed. First, it should be noted that the distribution of PTIN within this group could not be considered normal. The distribution is shown in Figure 2. Therefore, subsequent statistical analyses were performed with nonparametric tests that do not require the normality assumption that is usually used in parametric tests. For instance, to test for the correlation between the variables, we used Spearman's  $r$  instead of the classical Pearson's  $r$  coefficient.

Thus, correlation analysis with the LVM/height<sup>2.7</sup> showed  $r = -0.72$  ( $P < 0.0001$ ) for the PTIN (Figure 3A),  $r = 0.41$  ( $P < 0.001$ ) for the systolic BP load (Figure 3B), and  $r = 0.47$  ( $P < 0.001$ ) for the diastolic BP load (Figure 3C). The correlation between LVMI and PTIN was markedly higher.

Other correlations obtained in the study are presented in Table 2. It should be noted that the PTIN has more significant correlation coefficients with LVMI than the average PWV per day or its variability.

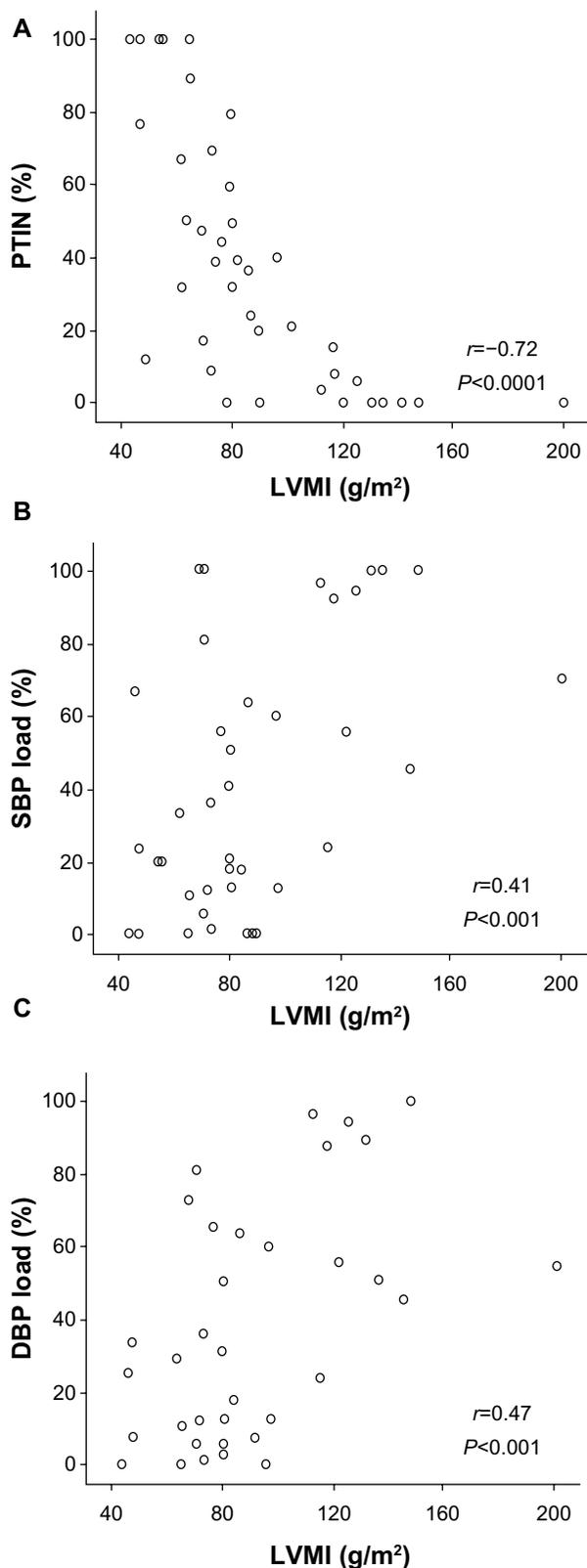
Important results were also obtained when PTIN was compared in patients with and without LVH. Figure 4 shows PTIN in 24-hour awake and asleep periods in these patients. As we can see, the boundaries of the PTIN percentile limits for the "asleep" period in these subgroups do not intersect. There are high significance levels (Yates corrected  $\chi^2 = 34.2$ ,  $P < 0.001$ ) if we construct a two-by-two table for awake and asleep periods in the subgroups listed above.



**Figure 2** Histogram of PTIN distribution – observed frequencies and expected normal curve.

**Note:** Pulse Time Index of Norm.<sup>2,22</sup>

**Abbreviation:** PTIN, Pulse Time Index of Norm.



**Figure 3** Correlation between the LVMI ( $g/m^2$ ) and: (A) the PTIN (%), (B) the SBP load (%), and (C) the DBP load (%).

**Notes:** Pulse Time Index of Norm.<sup>2,22</sup>

**Abbreviations:** DBP, diastolic blood pressure; SBP, systolic blood pressure; LVMI, left ventricular mass index; PTIN, Pulse Time Index of Norm.

**Table 2** The correlations between the echocardiographic data and the BPLab Vasotens® (Petr Telegin Company, Nizhny Novgorod, Russian Federation) indices

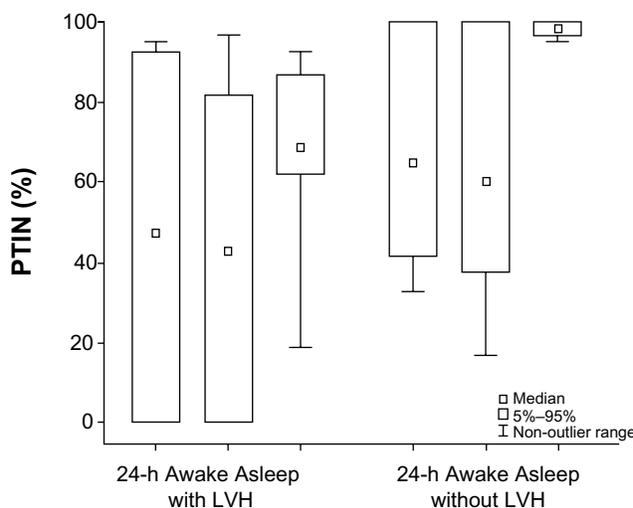
	LVM/height <sup>2.7</sup>		LVM/BSA	
	r	P-value	r	P-value
PTIN	-0.72	0.0001	-0.67	0.0001
Mean 24-hour PWV	0.32	0.01	0.32	0.01
Variability of PWV	0.12	>0.05	0.12	>0.05
SBP load	0.41	0.001	0.37	0.01
DBP load	0.47	0.001	0.37	0.01
Mean SBP	0.14	>0.05	0.15	>0.05
Mean DBP	0.29	>0.05	0.19	>0.05

**Note:** Pulse Time Index of Norm.<sup>2,22</sup>

**Abbreviations:** BSA, body surface area; DBP, diastolic blood pressure; LVM, left ventricular mass; PTIN, Pulse Time Index of Norm; PWV, pulse wave velocity; SBP, systolic blood pressure.

### Discussion

LVH is the most commonly assessed target organ effect of hypertension, and it is associated with a significantly increased cardiac risk in adults.<sup>15</sup> Several studies have shown that LVH, as with other markers of target organ damage, correlates with ambulatory BP more closely than with office BP.<sup>16,17</sup> A number of additional indices that might be derived from the ABPM recordings have been investigated; however, their added predictive value is not clear, and they should be regarded as experimental.<sup>1</sup> Some studies support the usefulness of circadian BP rhythm (a dipping pattern, morning BP) in predicting organ damage.<sup>18,19</sup> Other studies show the usefulness of the BP load in predicting organ damage.<sup>6,7,20</sup> In this present study, we obtained a similar correlation between the BP load and



**Figure 4** Medians, limits of the fifth and 95th percentiles and non-outlier range of PTIN according to 24-hour awake and asleep periods in patients with and without LVH.

**Notes:** Pulse Time Index of Norm.<sup>2,22</sup>

**Abbreviations:** LVH, left ventricular hypertrophy; PTIN, Pulse Time Index of Norm; h, hour.

the LVMI. One study has also shown an association of the ambulatory arterial stiffness index with the LVMI.<sup>21</sup>

Considering the above studies, our results from the PTIN study are very important. The correlation with the LVMI appears to be the highest among the correlations in similar studies of additional ABPM indexes. A difference can be seen in the correlations of the mean PWV with the LVMI ( $r=0.32$ ) and of the PTIN with the LVMI ( $r=-0.72$ ). In a comparison of recordings with similar average PWV levels, the differences in the PTIN can be largely explained by the differences in the PWV variability. Finally, the correlation of the PTIN of the “asleep” period with the presence of LVH is quite significant.

Our study has some limitations, which might have affected the results. Because the distribution of the PTIN is non-normal, the adjustment of the correlation between PTIN and LVM using analysis of variance or analysis of covariance is not possible. Perhaps the correlation differs across age groups or in patients with varying clinical parameters.

It is evident that only an event-based longitudinal study can provide an indisputable answer to the question of the clinical relevance of additional ABPM indices. Our previous work on the reliability of PTIN shows its good repeatability.<sup>22</sup> Thus, given the above results, we believe that the PTIN especially during the “asleep” period should also be considered in forthcoming research.

## Conclusion

The PTIN generated by the Vasotens technology can be recommended as an indicator of end organ damage resulting from hypertension.

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## Disclosure

BPLab® ABPM systems allowed NNK and EAG to participate in a previous scientific competition (2008–2012) organized by the manufacturer, Petr Telegin Company, in the Russian Federation. The BPStat® software was provided to INP and AVO by the manufacturer (Petr Telegin Company). The other authors report no conflicts of interest in this work.

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