Journal of Clinical Monitoring and Computing (2004) 18: 333–342

PULSE TRANSIT TIME BY R-WAVE-GATED INFRARED PHOTOPLETHYSMOGRAPHY: REVIEW OF THE LITERATURE AND PERSONAL EXPERIENCE

Jochanan E. Naschitz, MD,[1] Stanislas Bezobchuk, MD,[1] Renata Mussafia-Priselac, MD,[1] Scott Sundick, MD,[1] Daniel Dreyfuss, MD,[1] Igal Khorshidi, MD,[1] Argyro Karidis, MD,[1] Hagit Manor, MD,[1] Mihael Nagar, MD,[1] Elisabeth Rubin Peck, MD,[1] Shannon Peck, MD,[1] Shimon Storch, MD,[2] Itzhak Rosner, MD,[3] and Luis Gaitini, MD[4]

Naschitz JE, Bezobchuk S, Mussafia-Priselac R, Sundick S, Dreyfuss D, Khorshidi I, Karidis A, Manor H, Nagar M, Peck ER, Peck S, Storch S, Rosner I, and Gaitini L. Pulse Transit Time by R-wave-gated Infrared Photoplethysmography: Review of the Literature and Personal Experience.

J Clin Monit 2004; 18: 333–342

ABSTRACT. Objective. Pulse transit time (PTT) is the time it takes a pulse wave to travel between two arterial sites. A relatively short PTT is observed with high blood pressure (BP), aging, arteriosclerosis and diabetes mellitus. Most methods used for measuring the PTT are cumbersome and expensive. In contrast, the interval between the peak of the R-wave on the electrocardiogram and the onset of the corresponding pulse in the finger pad measured by photoplethysmography can be easily measured. We review herein the literature and impart the experience at our institution on clinical applications of R-wave-gated photoplethysmography (RWPP) as measurement of PTT. **Methods.** The MEDLINE data base on clinical applications of RWPP was reviewed. In addition, studies performed in the author's institution are presented. **Results.** When used as a surrogate for beat-to-beat BP monitoring, RWPP did not meet the level of accuracy required for medical practice (two studies). RWPP produced accurate and reproducible signals when utilized as a surrogate for intra-thoracic pressure changes in obstructive sleep apnea, as well as BP arousals which accompany central sleep apnea (five studies). In estimation of arterial stiffness, RWPP was unsatisfactory (one study). In assessment of cardiovascular reactivity, abnormal values of RWPP were noted in autonomic failure (one study), while disease-specific reactivity patterns were identified utilizing a method involving RWPP (two studies). **Conclusions.** In clinical practice, sleep-apnea may be accurately monitored by RWPP. RWPP seems to reflect autonomic influences and may be particularly well-suited for the study of vascular reactivity. Thus, further descriptions of disease-specific cardiovascular reactivity patterns may be possible with techniques based on RWPP. Other clinical uses of RWPP are investigational.

KEY WORDS. infrared photoplethysmography, blood pressure measurement, arterial stiffness, sleep apnea, dysautonomia.

INTRODUCTION

Pulse transit time (PTT) refers to the time it takes a pulse wave to travel between two arterial sites [1, 2]. The speed at which the arterial pressure wave travels is directly proportional to blood pressure (BP). With an acute rise in BP, vascular tone increases – the arterial wall becomes stiffer-causing the PTT to shorten. In contrast, when the BP falls there is relaxation of vascular tone and the PTT increases [1–4]. In addition, arteries stiffen with age, arteriosclerosis and diabetes mellitus, also resulting in a shortening of the PTT [5–9].

Several methods have been used to measure the PTT, most commonly Doppler ultrasound, aplanation tonometry and photoplethysmography [3, 10–13]. Doppler

From the [1]Departments of Internal Medicine A, [2]Nephrology, [3]Rheumatology, and [4]Anesthesiology, Bnai-Zion Medical Center and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

Received 26 April, 2004, and in revised form 17 August, 2004. Accepted for publication 1 October, 2004.

Address correspondence to Jochanan E. Naschitz, MD, Department of Internal Medicine A, Bnai Zion Medical Center, Haifa 31048, P.O. Box 4940, Israel.
E-mail: naschitz@tx.technion.ac.il.

ultrasound and tonometry can detect the pulse pressure within the artery, permitting the measurement of the PTT between two points of an arterial section. These methods are limited by noise and imprecise estimation of the distance between two arterial sites [14]. Photoplethysmography (PPG) utilizes an infrared optical transducer which produces a signal associated with the change in the volume of red blood cells in the microvascular bed with each pulse. This signal is induced by the combined volume and flow changes in the most superficial layers of the skin, approximately of 1 mm thickness [15, 16]. The main sites where the PPG signal can be obtained are the tissue pads of the ears, fingers and toes [13]. The equipment needed is commercially available, relatively cheap, and portable [1]. Detailed descriptions of instruments, filters, methods for signal smoothening to attain noise reduction, data storing, and data processing can be found in the literature [1, 2, 17, 18].

The interval between the peak of the R-wave on the electrocardiogram and the onset of the corresponding PPG pulse can serve as a measurement of PTT. This method was called by us 'R-wave-gated photoplethysmography' (RWPP). To demarcate the arrival of the pulse wave, either the foot of the systolic increase of the signal, the 25%, 50% or the maximum height of the pulse wave is identified, depending on which equipment is used [1, 2, 19, 20]. Strictly speaking, such measurements cannot provide the pulse wave velocity, since the pulse velocity changes along the arterial conduit as wall thickness and diameter varies [2, 21]. Nevertheless, it has been suggested that the simplicity of its measurement could make the RWPP a useful investigational tool [1, 17–19].

In the present study we review the literature on clinical applications of RWPP and summarize our experience in its use.

METHODS

The technique of R-wave-gated infrared photoplethysmography (RWPP) as utilized in our institution has been described in detail elsewhere [22, 23]. Testing was conducted from 8:00 to 11:00 a.m. in a quiet environment and at a constant room temperature of 22–25 °C. The patients were restricted from smoking and caffeine ingestion 6 h prior to the examination. Intake of food and medications with sympathomimetic activity was prohibited on the morning of study. The subject were supine, the right forearm and hand supported by a cast and suspended with a sling around their neck, the fingers pointed to the midaxillary line at the level of the fourth intercostal space. The electrocardiogram (ECG) and photoplethysmography (PPG) were recorded on a Datex-Engstrom Cardiocap^{TM} II instrument (Datex Instrumentation Corporation, Helsinki, Finland) connected to the Biopac MP 100 data acquisition system (Biopac, Santa Barbara). The photoelectric sensor of the PPG was placed on the distal phalanx of the second or third finger. The hand was held in a relaxed semi-open position, with the palm turned downward, and fixed with adhesive strips, taking care not to apply pressure to the PPG transducer. The Cardiocap^{TM} II operates with two light-emitting diodes, producing beams at red and infrared frequencies (660 and 940 nm, respectively) on one side and a sensitive photodetector on the other side. The emitting diodes work in sequence. The light absorbed by non-pulsatile tissues is constant. The non-constant absorption is the result of arterial pulsation. The sensitive photodetector generates a voltage proportional to the transmitted light. Very low power is necessary to obtain a satisfactory signal and no appreciable heating is produced by the emitter. In addition, the receiver is almost insensible to ambient light. The PTT is automatically computed on the AcqKnowledge software and the tracings are continuously displayed on the computer screen. The computer program identifies the PTT as the time interval between the peak of the electrocardiographic R-wave and the peak of the pressure wave at the finger, as measured by PPG. A sample rate of 500 data points per second provided 1/500 Hz resolution for the HR and PTT measurements.

A typical RWPP tracing is shown in Figure 1. Clinically relevant changes in BP are usually associated with concomitant changes in the PTT. Specifically, a rise in BP is associated with shortening in PTT over several cardiac cycles and a lasting drop in BP is associated with lengthening in PTT over several cardiac cycles, as illustrated. We utilized the term 'tall cluster' to describe grouped spikes of PTT (increased PTT) that were usually associated with hypotensive events.

Recognition of artifacts represents a major difficulty in RWPP measurement [1]. Artifacts are almost always due to interference with the photoplethysmographic signal at the finger but can also occur when chest wall movement disturbs the ECG recordings. Such artifacts are best screened out by manual signal scoring. But when automatic scoring is used, spurious interpretation may result [1]. Brief deliberate finger movements produce isolated, tall PTT spikes, while or clusters of tall PTT spikes ('tall clusters') occur when movements are repeated and prolonged. Tall clusters are also produced by applying external compression on the transducer, by defective transducer attachment, or when the transducer is disconnected. These artifacts can be avoided only partially by adequate support of the patient's hand and forearm and by securing the finger and transducer to the supporting cast. In our experience with the method as utilized in our laboratory, PTT less than 0.2 s in normotensive subjects usually

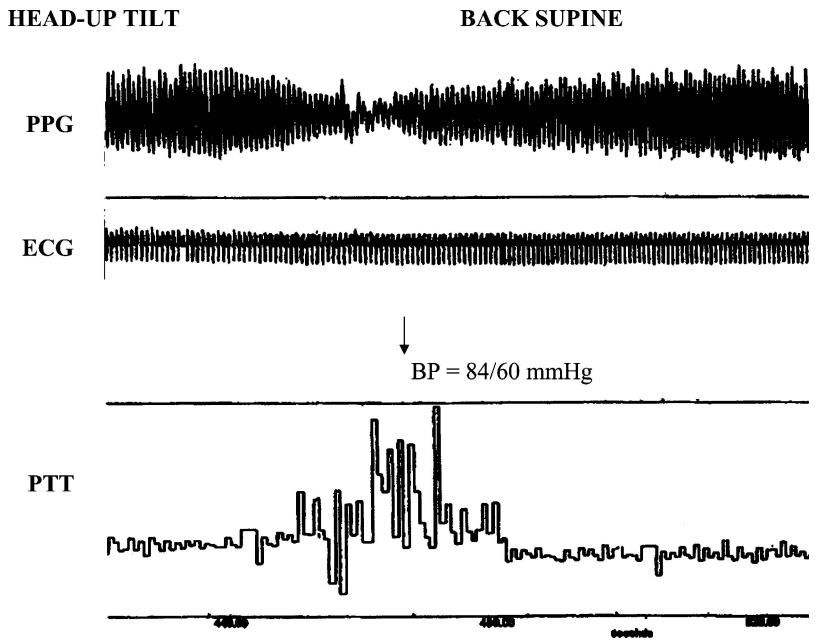

Fig. 1. A lasting drop in BP is associated with a concomitant increase in PTT over several cardiac cycles.

represents artifacts induced by finger movements. PTT values greater than 0.4 s are likely artifacts, when occurring singly or in couplets, but usually express an authentic decrease in BP when occurring in clusters of five or more spikes.

Review of the literature

Publications were reviewed for the following applications of RWPP: 1) As a surrogate for beat-to-beat monitoring of the BP; 2) In diagnosis and monitoring of sleep apnea; 3. For assessment of cardiovascular reactivity; 4) In estimation of arterial stiffness. The following index terms were searched in the MEDLINE data base: 'infra-red photoplethysmography' in combination with each one of the following: 'blood pressure', 'head-up tilt', 'Valsalva maneuver', 'ergometry', 'exercise stress test', 'sleep apnea', 'cardiovascular reactivity', 'baroreflex', 'autonomic nervous', 'dysautonomia', 'neuropathy', 'arterial stiffness', 'arterial compliance', 'pulse transit time' or 'pulse wave velocity'. The reference standard to which RWPP measurements were compared varied according to the clinical situations and included intra-arterial BP measurement, manual BP measurement by mercury column sphygmomanometry, beat-to-beat BP with the Finapress instrument, pulse wave velocity by aplanation tonometry or intra-esophageal pressure.

RESULTS

RWPP as a surrogate for beat-to-beat BP changes

RWPP has been studied for its value as a BP surrogate in monitoring changes during treadmill electrocardiography, with acceptable results in one study [24]. In another study [25], RWPP served as a surrogate for beat-to-beat BP in monitoring critically ill infants and children, showing good correlation with systolic BP ($r = 0.73$). Correlation was poorer with mean BP ($r = 0.68$) and diastolic BP ($r = 0.61$). In this latter work, RWPP as a surrogate for BP has not met the standard of accuracy required for clinical usage.

We evaluated RWPP as a surrogate BP measure in the recognition of hypotensive events during the head-up tilt test. The plethysmogram was recorded from the second or third finger of the right hand while BP was measured on the left arm with the aid of a mercury column sphygmomanometer [26]. Corresponding to each BP measurement, an average of 10–20 successive PTT values were recorded. Their average value was calculated and referred to the concurrent BP. Two-hundred and sixty paired PTT and BP values were analyzed. The average PTT value was 0.28 s ($SD = 0.065$), the average systolic BP was 123 mmHg ($SD = 21$ mmHg), and the average diastolic BP was 78 mmHg ($SD = 14$ mmHg). There was a significant inverse correlation between PTT and systolic BP ($p = 0.0013$)

and between PTT and diastolic BP ($p < 0.0001$). In individual readings, however, BP changes were not consistently associated with PTT changes. Thus, a drop in systolic BP by 30 mmHg or greater was not consistently associated with the expected proportional lengthening in PTT. Instead, the PTT change was in the range −5 to +320%.

In a subsequent study, we evaluated the value of PTT 'tall clusters' in predicting hypotensive events on head-up tilt. The PTT recordings of 100 consecutive patients who underwent a head-up tilt test for suspected neurally mediated syncope were analyzed by observers blinded to the patients' BP data. 'Tall clusters' were defined when three criteria were met: a) PTT amplitude exceeded 0.4 s; b) five or more such tall spikes occurred during a 15 s interval; c) heart rate exceeded 20 beats per minute during the spike cluster (for the purpose of excluding periods of asystole). Twenty-four patients developed hypotensive events during tilt with 'tall clusters' seen on PTT tracings in 13. Thus, the sensitivity of 'tall clusters' for hypotensive events was only 42%, wholly unsatisfactory, despite a specificity of 96%.

Digital photoplethysmography has also been used as a surrogate for beat-to-beat BP changes during the Valsalva maneuver, demonstrating a striking similarity to invasively recorded arterial BP [27]. During the Valsalva strain, intrathoracic pressure is voluntarily increased to 40 mmHg with consequent decrease in venous return as well as in BP. Occurrence of severe hypotension in this setting is prevented by reflex arteriolar constriction. In cases of autonomic failure this reflex is abolished and a severe drop in BP may ensue. Monitoring BP changes during the Valsalva maneuver is typically performed with a Finapress volume clamp instrument [28]. We used the RWPP method instead. Occurrence of 'tall clusters' at the end of the Valsalva strain phase indicated a persistent fall in BP, characteristic of sympathetic vasoconstrictor failure (Figure 2). At this point, the use of PTT as a surrogate for beat-to-beat BP during the Valsalva maneuver must still be considered experimental and requires further validation.

Recently, Chen and associates [20] designed a computer program that specifically processes the high frequency domain of the RWPP in order to track the systolic BP. Intermittent calibration of the instrument with oscillometric BP measurements permitted accurate estimates of the systolic BP based on RWPP data. By this method, the correlation coefficient of estimated and invasively measured systolic BP was 0.97 ($SD = 0.02$) in the 20 patients studied [20]. Confirmatory studies, each evaluating a few patients, produced similarly good results [29]. Recently, Chen's device has been incorporated into the Collin Press-Mate advantage® monitor with the 'Haste' algorithm (Colin Co., Japan) and is commercially available.

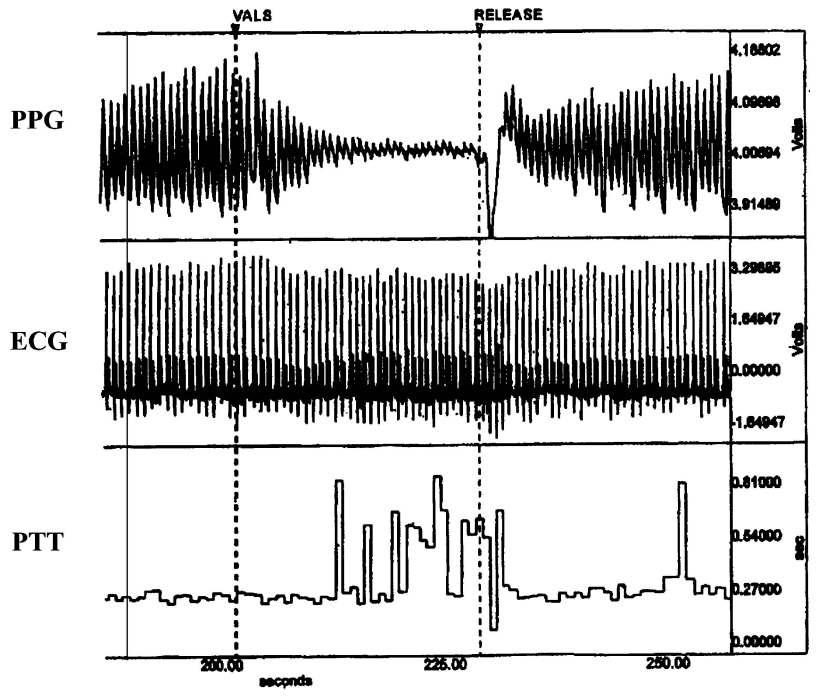

Fig. 2. Occurrence of 'tall clusters' at the end of Valsalva strain in a patient with autonomic failure.

Diagnosing sleep apnea

When an individual carries out an inspiratory effort against a threshold valve, negative intra-thoracic pressure develops and the BP decreases, accompanied by lengthening of the PTT [30]. In a similar manner, patients with obstructive sleep apnea episodically develop a negative intra-thoracic pressure during their hypopneic/apneic episodes, during which the PTT lengthens progressively [1, 31–33]. In contrast, in central apnea arousal from sleep occurs, associated with a sudden rise in BP and decrease in PTT. Accordingly, clusters of tall PTT spikes are markers of obstructive sleep apnea while sustained decreases in PTT over 5 or more pulse cycles are markers of central sleep apnea [33–35]. By recognizing these two patterns on RWPP tracings, apneic episodes can be consistently tracked and obstructive sleep apnea can be clearly distinguished from central sleep apnea with 95% inter-observer agreement [34]. Thus, RWPP lends itself to domiciliary use in the assessment of patients with disturbed sleep, offering a number of advantages over more conventional sleep-monitoring methods [1].

Evaluation of arterial stiffness

Arterial stiffness increases with age, diabetes mellitus, hypercholesterolemia, hypertension and end-stage renal disease [36]. Since changes in arterial stiffness may precede the clinical manifestations of cardiovascular disease, indices of arterial stiffness may be utilized to monitor the preclinical progression of arteriolosclerosis [37]. Several techniques have been applied to this end: ultrasound [38] or magnetic resonance imaging [39] are used to record serial images of the arterial lumen. The difference between the maximum and the minimum arterial lumen during the cardiac cycle is considered to reflect the difference between the maximum and minimum BP along the cycle. Based on these measurements, an equation is derived to compute the arterial stiffness. Aplanation tonometry [10] is used to record pressures at the radial or carotid arteries and estimate the systemic arterial stiffness. Arterial stiffness can also be derived from measurements of the PTT. Invasive or noninvasive methods are used to measure either flow or pressure waves. Readings are taken at two separate sites or by gating separate recordings to the R-wave of the electrocardiogram. This technique has been validated, confirmed to be reproducible and has been widely employed in research [18, 37, 40]. The relative inaccessibility of central arteries stands as alimitation of this methodology, frequently necessitating the surrogate use of adjacent superficial arteries.

We compared measurements of RWPP at fingers and toes in 20 young healthy subjects with those performed in 40 patients with atherosclerotic cardiovascular disease (Naschitz et al., personal communication). The latter group included subjects with one ore more of the following: arterial hypertension ($n = 26$), myocardial infarction ($n = 21$), intermittent claudication of the calves ($n = 6$), ischemic stroke ($n = 9$). Results of the PTT measurements by RWPP are shown in Table 1. As seen, values did not differ significantly between the groups. These data, then, do not support a role for RWPP as a marker of arteriosclerosis. These results are in line with other studies which have shown that the pulse wave velocity correlates better with age and atherosclerosis than does RWPP [18, 41].

Table 1. PTT measurement by RWPP in healthy young subjects versus elderly patients presenting overt atherosclerotic cardiovascular vascular disease (ASCVD)

Patient characteristics	Healthy ($n = 20$)	ASCVD ($n = 40$)	p value
Age (years)	34.04 (7.4)	70.9 (10.7)	<0.0001
Gender: F/M	12/8	21/19	NS
Height (cm)	170.2 (6.5)	167.3 (9.4)	NS
Sitting systolic BP (mmHg)	110 (13.6)	128.4 (19.5)	0.0021
Sitting diastolic BP (mmHg)	67.1 (8.5)	73.2 (9.3)	0.0399
Sitting heart rate (bpm)	79.7 (12.4)	73.4 (15.6)	NS
RWPP right toe (s)	0.348 (0.02)	0.331 (0.034)	NS
RWPP left toe (s)	0.344 (0.022)	0.326 (0.035)	NS

Note. ASCVD: atherosclerotic cardiovascular disease. Values in parentheses represent standard deviation.

Study of cardiovascular reactivity

Spontaneous fluctuations in HR and BP are attributed to autonomic nervous system influences [42, 43]. In the same way, the PPG signal may be influenced by autonomic nervous activity. Consistency between fluctuations of the power spectra of HR and BP and finger photoplethysmography signals has been demonstrated [44–47].

The head-up tilt test (HUTT) has been widely used in the assessment of autonomic function [47]. The fast response of BP and HR to acute stimuli is under autonomic nervous control and thus BP and HR measurements during orthostatic challenge can be used as one measure of cardiovascular autonomic activity, providing there is no evidence of organic heart disease, venous insufficiency or hypovolemia [47]. By applying the head-up tilt test to the study of autonomic function in a group of patients with chronic

fatigue syndrome, a disease-specific cardiovascular reactivity pattern was discerned in the large majority. This observation was made possible by use of a new technique for analysis of the cardiovascular signals [48, 49]. Successive improvements of the technique led to development of the 'Fractal & Recurrence Analysis-based Score' (FRAS) [22, 23]. The FRAS includes data acquisitioning of HR and the RWPP on a beat-to-beat basis during 10 min of recumbence and an additional 600 cardiac cycles of head-up tilt, i.e. 5–10 min. Such a short tilt is usually better tolerated than the 30 min required for the standard HUTT. Next, HR and PTT time-series are processed by image analysis methods (Figures 3 and 4). Multivariate analysis is used to derive independent predictors of the cardiovascular reactivity in a patient group against comparison groups. Based on these predictors, an equation is formulated to calculate a linear discriminant score (DS) which characterizes the study group. The RWPP data proved indispensable to the definition of specific cardiovascular reactivity patterns. When the FRAS was applied to differentiate the cardiovascular reactivity of chronic fatigue syndrome patients from other populations, two RWPP variables along with three HR variables were found to be independent predictors of the cardiovascular reactivity in the chronic fatigue syndrome group [22]. Similarly, RWPP was vital to the description of disease-specific cardiovascular reactivity patterns in neurally mediated syncope [50] (Figure 5). Attempt to rely solely on HR and intermittent BP measurements, without use of RWPP, to define disease-specific cardiovascular reactivities were not successful (Naschitz et al., personal communication).

DISCUSSION

The speed at which the arterial pressure wave travels is directly proportional to the BP. Thus, the hypothesis has been advanced that measurement of the PTT could serve as an

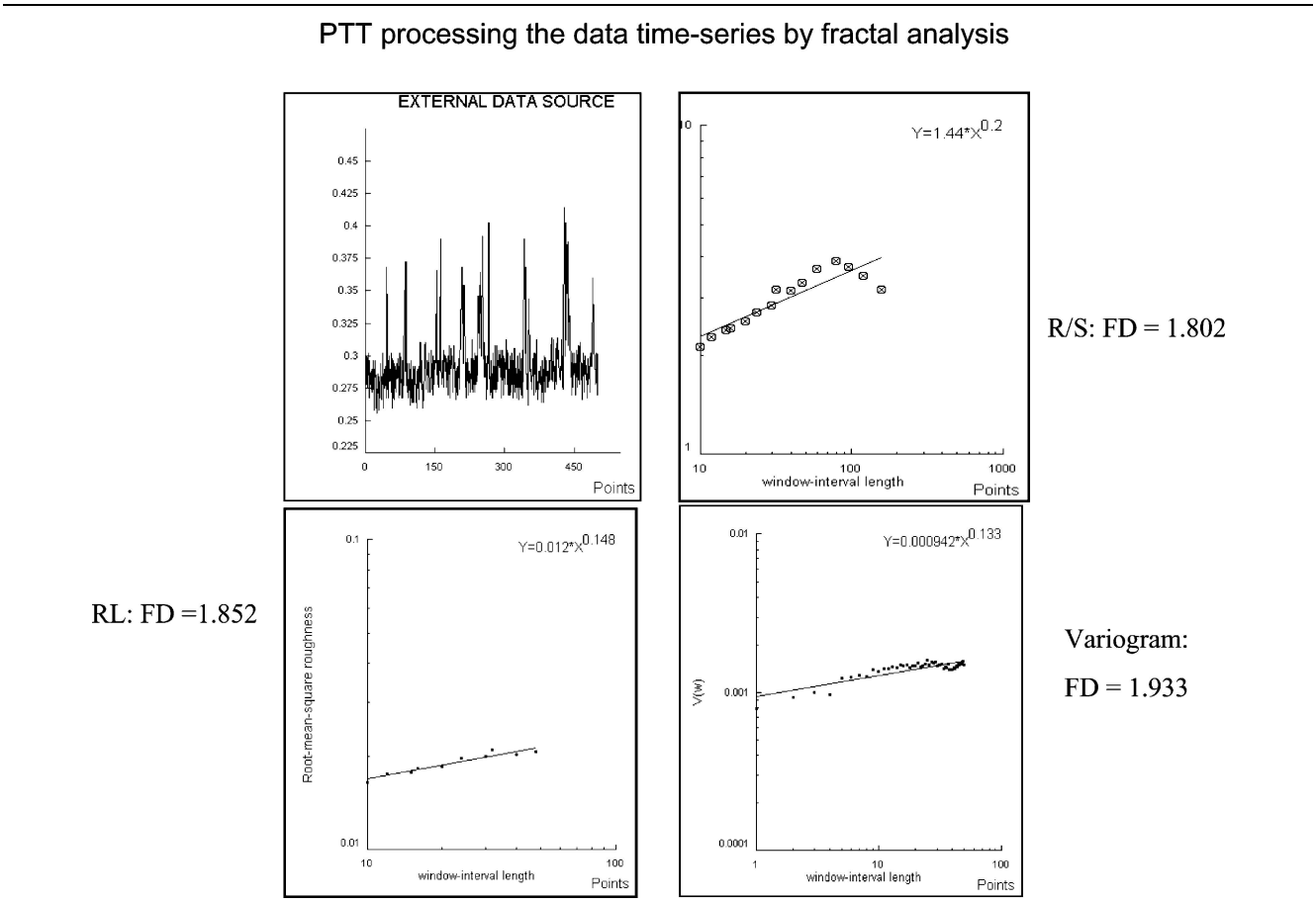

Fig. 3. Processing PTT time series by the method of fractal analysis. The external data source was a series of 500 consecutive PTT measurements and served to compute the fractal dimension (FD). Three methods for computing the FD are illustrated, the R/S, roughness-length and variogram. Each method produced a different result. By multivariate analysis, FD best as independent predictor of the patients' cardiovascular reactivity was identified.

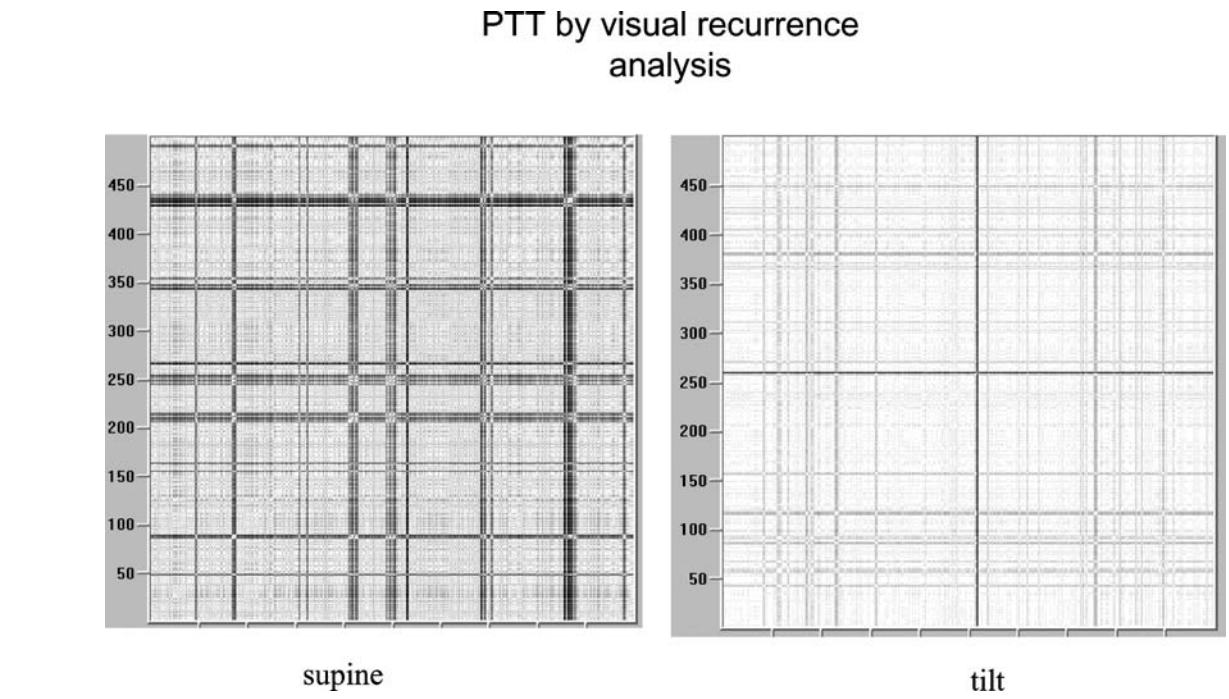

Fig. 4. Recurrence analysis: the external data source of PTT measurements (previously shown in Fig. 3) was assessed by the method of recurrence analysis. The visual recurrence plot in this figure permits easy recognition of the change in pattern that occurred when the patient was tilted. Subsequent quantitative analysis of the plot identified numerical measures of the PTT variability (not shown here).

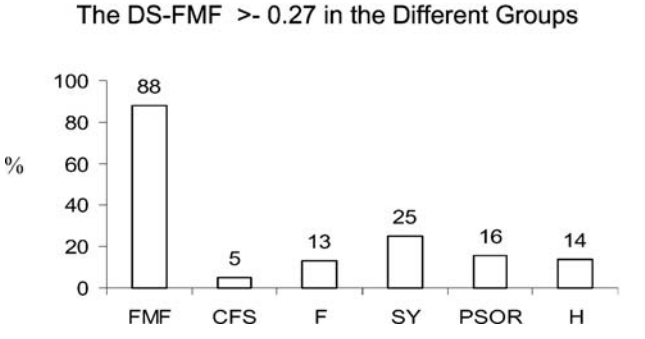

Fig. 5. A discriminant score (DS) cut-off > −0.27 differentiated FMF from all other patients with 88% sensitivity and 90.1% specificity. Based on the methods of fractal and recurrence quantitative analysis of HR and PTT, the DS was set to recognize the cardiovascular reactivity in FMF patients as against the reactivity in a mixed group of control patients. FMF – Familial Mediterranean Fever (n = 17), CFS – chronic fatigue syndrome (n = 20), F – non-CFS fatigue (n = 15), SY – neurally mediated syncope (n = 21), PSOR – psoriatic arthritis (n = 19), H – healthy (n = 20).

estimate for the BP. Among several methods available to measure the PTT, RWPP is cheap, technically undemanding and accessible in the setting of a general hospital. We reviewed the literature and the experience at our institution on clinical applications of RWPP.

RWPP applied as a surrogate for beat-to-beat BP monitoring showed a significant inverse correlation between the PTT and systolic BP as well as diastolic BP. In the individual case, however, BP changes were not consistently associated with PTT changes. These data are comparable to those of PTT when assessed with techniques other than RWPP [20, 51–56]. Thus, RWPP as a surrogate for beat-to-beat BP does not meet accuracy standards required for medical practice. On the other hand, RWPP was accurate and reproducible in indicating BP arousals which accompany central sleep apnea and as a surrogate for intra-thoracic pressure changes in obstructive sleep apnea [1, 31–35].

Use of RWPP as a measure of arterial stiffness was unsatisfactory in two published studies [18, 41], as well as in our experience. This may be due to limitations of the RWPP technique. Indeed, while pulse wave velocity can be accurately measured between two points along a large artery, the RWPP determination involves multiple indefinite features. These include the time interval between the R-wave on the electrocardiogram and the beginning of the pulse wave in the aorta, length of the arterial conduit from the heart to the finger pad, the changing velocity of the pulse wave along the arterial tree and autonomic influences on blood vessels, which may differ depending on size.

The novel finding of disease-specific cardiovascular reactivity patterns opens new directions in diagnosis and a better understanding of cardiovascular homeostasis. Our interest in RWPP for the study of autonomic nervous activity originated a few years back in the unexpected finding of a specific cardiovascular reactivity pattern in patients with chronic fatigue syndrome [48]. The existence of disease-specific cardiovascular reactivity patterns in chronic fatigue syndrome was confirmed by the technique of the FRAS, with beat-to-beat HR and RWPP recordings [22]. Subsequently, disease specific cardiovascular reactivity patterns were described in other disorders based on the same methodology [50]. The theoretical foundation for the possible advantage in utilizing RWPP for the study of cardiovascular reactivity came later, when data became available showing that skin microcirculation reflects systemic autonomic nervous influences [44–46]. The differential effect of sympathetic discharge, with constriction of selected vascular beds in specific circumstances further supported the utility of RWPP [57]. We speculated that finger photoplethysmography may be particularly suitable to detect autonomic nervous influences in the microcirculation and, at our institution, RWPP became an integral part of examinations by head-up tilt test. Further studies are needed to clarify this subject.

In conclusion, RWPP is inaccurate as a surrogate measure of BP and arterial stiffness but valuable, on the other hand, in the assessment of sleep-apnea and the evaluation of cardiovascular reactivity.

GLOOSSARY

BP = blood pressure
HR = heart rate
PPG = pulse plethysmography
PTT = pulse transit time
HUTT = head-up tilt test
RWPP = R-wave-gated photoplethysmography

REFERENCES

1. Smith RP, Argod J, Pepin JL, Levy PA. Pulse transit time: An appraisal of potential clinical applications. Thorax 1999; 54: 452–457.
2. Nitzan M, Khanokh B, Slovik Y. The difference in pulse transit time to the toe and finger measured by photoplethysmography. Physiol Meas 2002; 23: 85–93.
3. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995; 26: 485–490.
4. Nagai Y, Fleg JL, Kemper MK, Rywik TM, Earley CJ, Metter EJ. Carotid arterial stiffness as a surrogate for aortic stiffness: Relationship between carotid artery pressure-strain elastic modulus and aortic pulse wave velocity. Ultrasound Med Biol 1999; 25: 181–188.
5. O'Rourke MF. Isolated systolic hypertension, pulse pressure, and arterial stiffness as risk factors for cardiovascular disease. Curr Hypertens Rep 1999; 1: 204–211.
6. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens 2002; 15: 426–444.
7. O'Rourke MF, Hayward CS. Arterial stiffness, gender and heart rate. J Hypertens 2003; 21: 487–490.
8. Allen J, Murray A. Prospective assessment of an artificial neural network for the detection of peripheral vascular disease from lower limb pulse waveforms. Physiol Meas 1995; 16: 29–38.
9. van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, van Bortel LM. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: A population study. Hypertension 2000; 35: 637–642.
10. O'Rourke MF, Gallangher DE. Pulse wave analysis. J Hypertens 1996; 14: 147–157.
11. Lehmann ED, Hopkins KD, Rawesh A, Joseph RC, Kongola K, Coppack SW, Gosling RG. Relation between number of cardiovascular risk factors/events and noninvasive Doppler ultrasound assessments of aortic compliance. Hypertension 1998; 32: 565–569.
12. Lehmann ED, Hopkins KD, Gosling RG. Aortic compliance measurements using Doppler ultrasound: In vivo biochemical correlates. Ultrasound Med Biol 1993; 19: 683–710.
13. Jago JR, Murray A. Repeatability of peripheral pulse measurements on ears, fingers and toes using photoelectric plethysmography. Clin Phys Physiol Meas 1988; 9: 319–330.
14. Davies JI, Struthers AD. Pulse wave analysis and pulse wave velocity: A critical review of their strengths and weaknesses. J Hypertens 2003; 21: 463–472.
15. Bernardi L, Saviolo R, Spodick DH. Noninvasive assessment of central circulatory pressures by analysis of ear densitographic changes during Valsalva maneuver. Am J Cardiol 1989; 64: 787–792.
16. Challoner AVJ. Photoelectric plethysmography for estimating cutaneous blood flow. In: Rolfe P, ed. Non-invasive physiologic measurements. London: Academic Press, 1979: 125–151.
17. Argod J, Pepin JL, Smith RP, Levy P. Comparison of esophageal pressure with pulse transit time as a measure of respiratory effort for scoring obstructive nonapneic respiratory events. Am J Respir Crit Care Med 2000; 162: 87–93.
18. Bortolotto LA, Blacher J, Kondo T, Takazawa K, Safar ME. Assessment of vascular aging and atherosclerosis in hypertensive subjects: Second derivative of photoplethysmogram versus pulse wave velocity. Am J Hypertens 2000; 13: 165–171.
19. Allen J, Murray A. Similarity in bilateral photoplethysmographic peripheral pulse wave characteristics at the ears, thumbs and toes. Physiol Meas 2000; 21: 369–377.
20. Chen W, Tobahashi T, Ichikawa S, Takeuchi Y, Togawa T. Continuous estimation of systolic blood pressure using the pulse arrival time and intermittent calibration. Med Biol Eng Comput 2000; 38: 569–574.
21. Pitson D, Chhina N, Knijn S, van Herwaaden M, Stradling J. Mechanisms of pulse transit time lengthening during inspiratory effort. J Ambul Monit 1995; 8: 101–105.

22. Naschitz JE, Sabo E, Naschitz S, Rozenbaum M, Rosner I, Musafia-Priselac R, Shaviv N, Ahdoot A, Ahdoot M, Gaitini L, Eldar S, Yeshurun D. Fractal analysis and recurrence quantification analysis of heart rate and pulse transit time for diagnosing chronic fatigue syndrome. Clin Autonom Res 2002; 12: 264–272.
23. Naschitz JE, Rosner I, Shaviv N, Khorshidi I, Sundick S, Isseroff H, Fields M, Musafia Priselac R, Yeshurun D, Sabo E. Assessment of cardiovascular reactivity by fractal and recurrence quantification analysis of heart rate and pulse transit time. J Hum Hypertens 2003; 17: 111–118.
24. Barschdorff D, Erig M. Continuous blood pressure monitoring during stress ECG. Biomed Tech (Berl) 1998; 43: 34–39.
25. Wippermann CF, Schranz D, Huth RG. Evaluation of the pulse wave arrival time as a marker for blood pressure changes in critically ill infants and children. J Clin Monit 1995; 11: 324–328.
26. Training and certification of blood pressure observers. Hypertension 1983; 5: 610–614.
27. Weinman J, Ben-Yaakov S, Sapoznikov D. The application of photoplethysmography to the recording of Valsalva maneuver responses. Israel J Med Sci 1969; 5: 534–536.
28. Mathias CJ, Bannister R. Investigation of autonomic disorders. In: Mathias Ch J (ed.) Autonomic failure. A textbook of clinical disorders of the autonomic nervous system, 4th ed. Oxford, UK: Oxford Univeristy Press, 1999: 175–177.
29. Yano K, Kimora T, Sato Y, Nishiwaki K, Shimada Y. Delay time between the R-wave and maximum pulse wave upstroke reflects alterations in blood pressure. Anesthesiology 2002; 96: A491
30. Brock J, Pitson D, Strandling J. Use of pulse transit time as a measure of changes in inspiratory effort. J Ambul Monit 1993; 6: 295–302.
31. Pitson D, Chhina N, Knijn S, van Herwaaden M, Stradling J. Changes in pulse transit time and pulse rate as markers of arousal from sleep in normal subjects. Clin Sci (Lond) 1994; 87: 269–273.
32. Condos R, Norman RG, Krishnasamy I, Peduzzi N, Goldring RM, Rapoport DM. Flow limitation as a noninvasive assessment of residual upper-airway resistance during continuous positive airway pressure therapy of obstructive sleep apnea. Am J Respir Crit Care Med 1994; 150: 475–480.
33. Argod J, Pepin JL, Smith RP, Levy P. Comparison of esophageal pressure with pulse transit time as a measure of respiratory effort for scoring obstructive nonapneic respiratory events. Am J Respir Crit Care Med 2000; 162: 87–93.
34. Argod J, Pepin JL, Levy P. Differentiating obstructive and central sleep respiratory events through pulse transit time. Am J Respir Crit Care Med 1998; 158: 1778–1783.
35. Pitson DJ, Stradling JR. Autonomic markers of arousal during sleep in patients undergoing investigation for obstructive sleep apnea, their relationship to EEG arousals, respiratory events and subjective sleepiness. J Sleep Res. 1998; 7: 53–59.
36. Glasser SP, Arnett DK, McVeigh GE, Finkelstein SM, Bank AJ, Morgan DJ, Cohn JN. Vascular compliance and cardiovascular disease: A risk factor or a marker? Am J Hypertens 1997; 10: 1175–1189.
37. Mackenzie IS, Wilkinson IB, Cockcroft JR. Assessment of arterial stiffness in clinical practice. QJM 2002; 95: 67–74.
38. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, Heiss G. Arterial stiffness and the development of hypertension. The ARIC study. Hypertension 1999; 34: 201–206.
39. Resnick LM, Militianu D, Cunnings AJ, Pipe JG, Evelhoch JL, Soulen RL. Direct magnetic resonance determination of aortic distensibility is essential hypertension: Relation to age, abdominal visceral fat and in situ intracellular free magnesium. Hypertension 1997; 30: 645–649.
40. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. J Hypertens 1998; 16: 2079–2084.
41. Hasegawa M, Nagao K, Kinoshita Y, Rodbard D, Asahina A. Increased pulse wave velocity and shortened pulse transmission time in hypertension and aging. Cardiology 1997; 88: 147–151.
42. Bernardi L, Radaelli A, Solda PL, Coats AJS, Reeder M. Autonomic control of skin microvessels: Assessment by power spectrum of photoplethysmography. Clin Sci 1996; 90: 345–355.
43. Ackselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: Investigation by spectral analysis. Am J Physiol 1985; 249: H867–H875.
44. Malliani A, Pagani M, Lombardi F, Cerruti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991; 84: 482–492.
45. Nitzan M, Babchenko A, Khanokh B, Landau D. The variability of the photoplethysmographic signal – A potential method for the evaluation of the autonomic nervous system. Physiol Meas 1998; 19: 92–102.
46. Pitson DJ, Sandell A, van den Hout R, Stradling JR. Use of pulse transit time as a measure of inspiratory effort in patients with obstructive sleep apnoea. Eur Respir J 1995; 8: 1669–1674.
47. Wieling W, Karemaker JM. Measurement of heart rate and blood pressure to evaluate disturbances in neurocardiovascular control. In: Mathias ChJ (ed.) Autonomic failure. A textbook of clinical disorders of the autonomic nervous system, 4th ed. Oxford, UK: Oxford Univeristy Press, 1999: 198–210.
48. Naschitz JE, Sabo E, Naschitz S, Shaviv N, Rosner I, Rozenbaum M, Gaitini L, Ahdoot A, Ahdoot M, Priselac RM, Eldar S, Zukerman E, Yeshurun D. Hemodynamic instability in chronic fatigue syndrome: Indices and diagnostic significance. Semin Arthritis Rheum 2001; 31: 199–208.
49. Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Fields M, Isseroff H, Musafia Priselac R, Gaitini L, Eldar S, Zukerman E, Yeshurun D. Hemodynamic instability score in chronic fatigue syndrome (CFS) and non-CFS chronic fatigue. Semin Arthritis Rheum 2002; 32: 141–148.
50. Naschitz JE, Rosner I, Rozenbaum M, Fields M, Isseroff H, Babich JP, Zuckerman E, Elias N, Yeshurun D, Naschitz S, Sabo E. Disease-related phenotypes of cardiovascular reactivity as assessed by fractal and recurrence quantitative analysis of the heart rate and pulse transit time. Q J Med 2004; 97: 141–151.
51. Gribbin B, Streptoe A, Sleight P. Pulse wave velocity as a measure of blood pressure change. Psychophysiology 1976; 12: 86–90.
52. Geddes LA, Voelz MH, Babbs CF, Buirland JD, Tacker WA. Pulse transit time as an indicator of arterial blood pressure. Psychophysiology 1981; 18: 71–74.
53. Tanaka H, Sakamoto K, Kanai H. Indirect blood pressure measurement by the pulse wave velocity method. Med Electron Biol Eng 1984; 22: 13–18.
54. Lu W, Li H, Tao S, Zhang D, Jiang Z, Cui L, Tu J, Gou D. Research of the main elements influencing blood pressure

measurement by pulse wave velocity. Front Med Biol Eng 1992; 4: 189–199.
55. Wipperman CF, Schranz D, Huth RG. Evaluation of pulse wave arrival time as a marker for blood pressure changes in critically ill infants and children. J Clin Monit 1995; 11: 324–328.
56. Young CC, Mark JB, White W, DeBree A, Vender JS, Fleming A. Clinical evaluation of continuous blood pressure monitoring: Accuracy and tracking capabilities. J Clin Monit 1995; 11: 245–252.
57. Dampney RA, Coleman MJ, Fontes MA, Hirooka Y, Horiuchi J, Li YW, Polson JW, Potts PD, Tagawa T. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. Clin Exp Pharmacol Physiol. 2002; 29: 261–268.