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A. Hennig¹ · A. Patzak²

¹ SOMNOmedics GmbH, Randersacker

² AG Nierengefäßphysiologie, Institut für Vegetative Physiologie, Charité-Universitätsmedizin Berlin

Continuous blood pressure measurement using pulse transit time

Sleep medicine and sleep research are fast developing fields in medicine. One important reason for this is the discovery of causal interrelations between sleep apnea and cardiovascular diseases. Sleep apnea has a high incidence in males and females older than 45 years. It is associated with arterial hypertension, cardiac arrhythmia, sudden cardiac death, and stroke [24, 39]. Recent studies suggest a causal relationship between sleep apnea and arterial hypertension [46]. However, mechanisms of this interaction are not completely known. Studies suggest that intermittent hypoxia and reoxygenation [20] induce oxidative stress, activation of inflammation and endothelial dysfunction [50]. Together with activation of peripheral chemoreceptors and the sympathetic nervous system, this can lead to systemic arterial hypertension [32]. Until now, further elucidation of the mechanisms of this causal interaction between sleep apnea and hypertension was also limited by the difficulties to measure BP continuously and non-invasively during sleep.

Traditional cuff based methods using Korotkoff sounds or oscillometric methods do not measure BP continuously. These methods require inflation and following deflation of the cuff, which is time consuming and prevents continuous measurement. Furthermore, for reliable measurements, the interval between measurements should be at least 2 min [10]. Therefore, changes in BP, which are in the range of seconds to minutes, cannot be detected. Although limited in the short-term range, cuff-based ambulatory BP measurement allows detecting long-term changes in BP.

However, the arousal reaction can induce BP changes, which may hamper the discrimination of dipper or non-dipper character of night time BP.

Two methodically different methods of non-invasive and continuous BP measurement are available and work in practice: the method after Peñáz using a finger cuff and the more recently introduced method using pulse transit time (PTT).

The BP measurement based on the Peñáz principle

About 40 years ago Peñáz introduced a method for continuous and non-invasive measurement of BP based on the principle of vascular unloading [45]. For the first time, continuous recording was possible using an electropneumatic control loop. Peñáz's idea was implemented in several commercial apparatus. The measuring principle is as follows: The pulsatile blood volume of the finger of a patient is measured using infrared light. The light source and sensor are embedded in a finger cuff. The signal from the sensor, which transfers the changes in blood volume, regulates cuff pressure so that the vessel wall is unloaded. The cuff pressure corresponds to the intra-arterial BP. The system reacts sensitively to changes in arterial diameter and volume, respectively, and to vasoconstriction. Such situations lead to loss of the unloaded wall situation and initiate a re-calibration maneuver of the apparatus. Re-calibration is necessary to regain the set point of the system. During re-calibration, the system works in the open-loop mode and the measurement of

the BP is interrupted. Typical settings in which re-calibration frequently occurs are measurements during physical load, changes in the body position leading to increases or decreases in hydrostatic pressure, and temperature-induced changes in finger perfusion due to vasoconstriction or vasodilatation.

Peñáz's method was improved several times resulting in longer stability of the system and less frequent re-calibrations [29, 38, 41]. However, interruptions of the continuous measurement by calibration maneuvers cannot be completely prevented. They often occur during transient changes of BP. This is a disadvantage when considering that obtaining short-term BP fluctuation is the most attractive application of this method. Obviously, the interruption of the measurement due to re-calibration is one of the drawbacks of the system. Advanced systems using Peñáz's principle have been developed further to reduce the re-calibration maneuvers [18].

Continuous and non-invasive BP measurement using PTT

Theoretical background

PTT is defined as the time it takes the pulse wave to travel between two arterial sites within the same cardiac cycle. This time is related to the propagation velocity of the pulse wave. The physical conditions have been mathematically described by Moens and Korteweg [9, 61]. The pulse wave velocity is related to the elasticity of the arterial vessel (Young's modulus) by

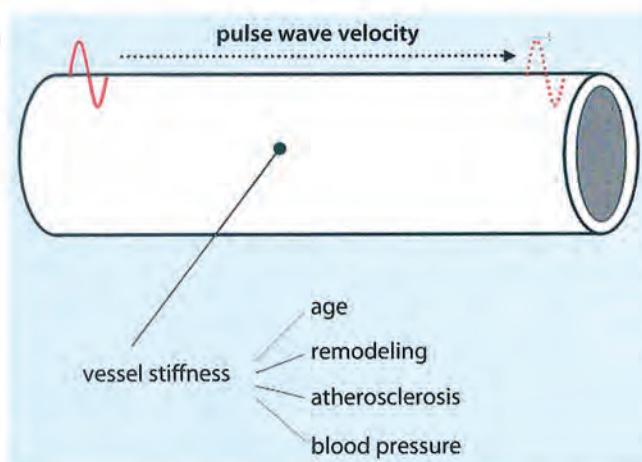


Fig. 1 ◀ Pulse wave velocity is related to the stiffness of the vessel. The greater the stiffness, the higher the pulse wave velocity. The stiffness of arteries is modulated by several factors such as age, vascular remodeling, atherosclerosis, and blood pressure

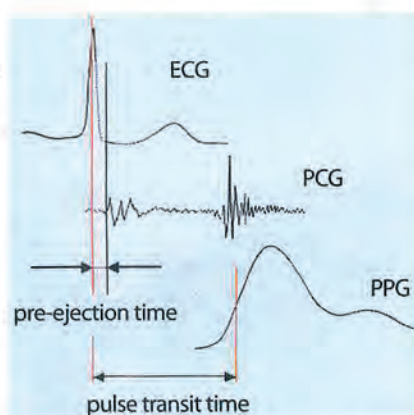


Fig. 2 ▲ Determination of PTT including the pre-ejection period. ECG electrocardiogram, PCG phonocardiogram, PPG photoplethysmogram

$$PWV = \sqrt{\frac{Eh}{\rho D}}$$

where PWV is the pulse wave velocity, E the incremental Young's modulus, h is the arterial wall thickness, ρ is the density of the blood, and D is the diameter of the vessel. As a consequence, mainly intrinsic elastic properties of the arterial wall, remodeling, age, and BP determine the pulse wave velocity (■ Fig. 1).

Indeed, studies showed that age, gender, and cardiovascular risk factors, which are related to greater arterial stiffness, significantly correlate with the pulse wave velocity [37, 52]. In the last decade, the measurement of arterial stiffness became a useful tool for studying cardiovascular pathophysiology and effects of therapies [12, 15, 43, 57]. Also, a relation between pulse wave velocity and BP has been shown in human studies, which opens the possibility to measure BP non-invasively and continuously

[16, 68]. Studies showed that the PTT reflects short-term changes of BP and hemodynamic parameters [5, 28, 47, 54, 55]. Only one investigator did not find significant correlations between pulse wave velocity and BP [49]. Determination of absolute BP using PTT requires consideration of the individual vessel wall stiffness, which is independent from BP. This can be achieved by measuring the functional relation between the pulse wave velocity and the BP, thereby calibrating the BP measurement. Linear as well as non-linear relations between PTT and BP have been described [67]. However, determination of the individual relation between pulse wave velocity and BP is time consuming and not feasible in most clinical situations. It requires a protocol for stepwise increases in BP and several simultaneous measurements of the BP by PTT and a reference method. Thus, measurement of absolute BP using PTT is a challenge under clinical conditions. Recently, a method was developed, which requires just one calibration measurement. The study based on this method shows a good correlation of systolic BP measured by PTT and the cuff-based method [22].

Methods for determining PTT

Detection site of the pulse wave

PTT used to determine BP is mostly determined as the period between the R wave of the electrocardiogram and the peripheral pulse wave (finger plethysmography, ■ Fig. 2). In some cases other signals have been used such as the cardiophonogram and the peripheral pulse wave. The arrangement used to determine PTT has consequences for the interpretation of the

results since different components of the vasculature have different elastic properties and pathologies. For example, in case of using the R wave of the electrocardiogram and the peripheral pulse, mechanical properties of large, middle sized, and small arteries contribute to the measured pulse wave velocity and PTT, respectively. The electrocardiogram and the peripheral volume pulse (plethysmography) are available in equipment for sleep diagnosis including screening devices. Therefore, additional placement of sensors is not necessary for the determination of PTT in these arrangements. Until now, there are no practical requirements stated in the literature regarding the technical equipment for determining PTT. However, some relevant parameters should be considered in order to provide reliable PTT values. These include little signal filtering, preferably high sampling rates and high signal resolution. Beside these factors, the phasing of the signals is premise for accurate PTT determination. As far as we know, there are no studies comparing the feasibility of the different diagnostic devices.

Pre-ejection period

The R wave of the electrocardiogram is an electrical signal that precedes the mechanical action of the heart. Consequently, in case of using the R wave determination of the PTT includes the pre-ejection period (■ Fig. 2). This period does not count to the pure PTT. The physiologically more correct signal for the detection of the beginning of the mechanical pulse would be the heart sound. Adequate detection of the heart sound is demanding and less reliable compared to the electrocardiogram. Further, it requires additional equipment and loads the patient. Therefore, the R wave is the preferred signal in the literature. The pre-ejection period correlates inversely with the sympathetic activation and heart rate, respectively, and therefore influences the PTT [2, 63]. Beside the detection site of the pulse wave individual parameters (e.g., height, age, and vessel properties) also strongly affect the PTT and therefore hamper the definition of PTT standard values. Depending on individual parameters and the pulse wave detection site PTT values range between 100 and 400 ms [4]. It was shown that ad-

ministration of norepinephrine can decrease the PTT by about 22 ms from baseline values of 260 ms, which corresponded to an increase of the calculated BP of 26 mmHg [44]. Salbutamol application induced preferential changes in diastolic BP (-31 mmHg) in this study [44]. These observations show that the pre-ejection period can significantly affect the PTT and this may limit the application of this method in patients receiving medications which influence the pre-ejection period.

Calculation of pulse wave velocity

The velocity of a mechanical impulse results from the time which it needs to cover a distance:

$$\text{velocity} = \frac{\text{distance}}{\text{time}}$$

In practice, this distance results from the interval between the beginning of the pulse wave at the heart and the peripheral site of pulse detection [14]. The formula is as follows when using a signal from the heart (e.g., R wave of the electrocardiogram) and the finger pulse (plethysmography):

$$PWV \text{ [cm/ms]} = \frac{BDC \cdot \text{height [cm]}}{PTT \text{ [ms]}}$$

where PWV is pulse wave velocity, BDC is body correlation factor, and height is the person's height in cm. The body correlation factor is 0,5 for adults. It corresponds to the distance from sternal notch to the tip of the middle finger. Several studies showed a significant correlation between arm span and body height along with small absolute differences between both measures [42, 58].

R wave and pulse wave detection

Numerous methods have been developed and applied for the detection of the R wave and the QRS complex, respectively. Algorithms of detection include differentiation of the signal [19], application of filters [27], or more sophisticated methods, for example neural networks [1, 35, 66] and wavelet coefficients [70]. Although most methods detect the R wave in non-disturbed leads of the electrocardiogram reliably, problems arise if the quality of the signal is poor (noise) or if the pattern of the electrocardiogram changes significantly. Thus, path-

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Abstract

Measurement of blood pressure (BP) during sleep is gaining in importance for clinical and scientific reasons. Diagnosis and follow-up of arterial hypertension requires BP measurement during sleep. Further, continuous BP measurements are necessary to elucidate the pathogenesis of sleep disturbances (e.g., sleep apnea), which are related to arterial hypertension. This review gives a short overview about cuff-based methods and methods for continuous and non-invasive BP measurement with a focus on sleep. The emphasis of this review is on the indirect measurement of BP using the pulse transit time (PTT). This method is based on the functional re-

lation between arterial wall stiffness, pulse wave velocity, and BP. It can be used for absolute BP measurement when combined with calibration. Recent validation and application studies of the BP measurement using the PTT suggest that this method can in principle be used for BP monitoring during sleep. It opens the possibility to study the control of BP during sleep.

Keywords

Sleep · Sleep apnea · Blood pressure · Pulse wave velocity · Validation of blood pressure measurement

Kontinuierliche Blutdruckmessung anhand der Pulstransitzeit

Zusammenfassung

Blutdruckmessungen im Schlaf gewinnen sowohl für klinische als auch wissenschaftliche Anwendungen eine immer größere Bedeutung. Diagnose und Verlaufsbeobachtungen der arteriellen Hypertonie schließen Untersuchungen des Blutdrucks im Schlaf ein. Insbesondere kontinuierliche Messungen sind für die weitere Aufklärung der Pathogenese von Schlafstörungen, die mit Hypertonie vergesellschaftet sind, von besonderem Wert. Das betrifft unter anderem das Schlafapnoe-Syndrom. Dieser Artikel gibt einen kurzen Überblick über die manschettenbasierten Methoden und eine neue Methode der kontinuierlichen nichtinvasiven Blutdruckmessung. Der Schwerpunkt liegt auf der indirekten Blutdruckmessung mittels Pulstransitzeit.

Die Methode basiert auf der funktionellen Beziehung zwischen der Steifheit arterieller Gefäße, der Pulswellengeschwindigkeit und dem Blutdruck. Unter Anwendung einer Ein-Punkt-Kalibrierung sind Messungen absoluter Blutdruckwerte möglich. Die bisher vorliegenden Validierungsstudien zeigen, dass dieses Verfahren für die kontinuierliche Blutdruckmessung im Schlaf prinzipiell geeignet ist und zur weiteren Aufklärung schlafbezogener Blutdruckregulation beitragen kann.

Schlüsselwörter

Schlaf · Schlafapnoe · Blutdruck · Pulswellengeschwindigkeit · Validierung der Blutdruckmessung

ological patterns of the electrocardiogram and cardiac arrhythmias may lead to inaccurate detection of the R wave and consequently to incorrect detection of the PTT. A reliable algorithm for R wave detection and an undisturbed lead of the electrocardiogram are the best requisites for sufficient detection of the PTT.

The peripheral pulse wave is also influenced by several factors. Breathing, ambient temperature, movements, and other factors influencing volume and sympathetic tone modulate the peripheral pulse significantly [6, 25, 65].

Methods for pulse wave analysis and detection, respectively, include threshold detection and sophisticated algorithms

such as Empirical Mode Decomposition (EMD), combination of derivative analysis, waveform averaging and rule-based logic, and other more [3, 8, 11, 26, 60]. Some algorithms may be superior for pulse wave detection. However, systematic analyses of the accuracy with regard to measuring the PTT have not been performed until now. The correlation between the systolic BP and the PTT was better when taking the foot of the peripheral pulse wave compared to the peak of the signal in a recent study [62]. Often, the arrival of the pulse wave in the periphery is defined as the fastest slope of the pulse wave (■ Fig. 2). The definition of the peripheral pulse wave arrival may influence PTT detection and the

Tab. 1 Representative validation studies for the PTT method

| Authors | Patients | Manipulations | Reference method | PEP | Calibration | Correlation factor for SBP | Correlation factor for DBP | Limits of agreement for SBP (mmHg) | Limits of agreement for DBP (mmHg) |
|--------------------------|---|--|---------------------------|------------------------------|----------------------------------|---|---|---|---|
| Young et al. [69] | 35 patients | Endotracheal anesthesia | Intra-arterial | | Off-set correction | – | – | –29.0 to 28.2 | –14.9 to 14.8 |
| Wippermann et al. [61] | 15 critically ill infants and children | | Intra-arterial | Included | – | 0.73 | 0.61 | – | – |
| Lutter et al. [33] | Patients | – | Intra-arterial | Included | – | 0.86 | – | 10.0 to –10.0 | – |
| Ahlstrom et al. [2] | 10 normal adults and dialysis patients | Lower body negative pressure and isometric contraction | Cuff-based Intra-arterial | Included as well as excluded | – | 0.80 | – | – | – |
| Payne et al. [44] | 12 healthy men | Drug application | Intra-arterial | Included Excluded | – | – | – | +17.0 to –17.0 | ±17.3 |
| Foo et al. [17] | 31 healthy adults | Postural changes | Cuff-based | Excluded | – | 0.82 (calculated from data) | – | – | – |
| Chen et al. [13] | Female patients | Anaesthesia | Cuff-based | Finger–toe distance | – | PWV and SBP: 0.4558 | PWV and DBP: 0.2719 | – | – |
| Wong et al. [64] | 14 healthy, normotensive men and women | Treadmill exercise | Cuff-based | Included | – | SBP – PTT: –0.92 | DBP – PTT: –0.38 | – | – |
| Wong et al. [62] | 41 healthy normotensive | Treadmill exercise | Cuff based | Included | – | SBP – PTT: –0.85 (foot of wave) –0.77 (peak of wave) | DBP – PTT: –0.36 (foot of wave) –0.39 (peak of wave) | – | – |
| Wagner et al. [59] | 24 healthy volunteers 112 patients with HF | Repeated measurements over 8 weeks | Cuff-based | Included | – | SBP – PTT: –0.73 SBP – PTT: –0.23 | – | – | – |
| Bartsch et al. [7] | 10 patients in intensive care unit, no hypotension, no arrhythmias 8 with hypotension 22 with arrhythmias | – | Intra-arterial | Included | Individual one-point calibration | – | – | 15.22 to –14.24 13.60 to –24.95 34.81 to –36.57 | 16.75 to –10.96 27.02 to –14.29 24.66 to –25.17 |
| Gesche et al. [22] | 50 male and female volunteers | Bicycle exercise | Cuff-based | Included | Individual one-point calibration | 0.83 | – | 19.8 to –19.8 | – |
| Hennig et al. [23] | 11 patients with apnea | Sleep, apnea related BP changes | Cuff-based | Included | Individual one-point calibration | – | – | 14.7 to –14.7 | – |
| Schmalgemeie et al. [53] | 64 patients | Positive airway ventilation | Cuff-based | Included | Individual one-point calibration | 0.95 | 0.96 | – | – |

PEP pre-ejection period, SBP systolic blood pressure, DBP diastolic blood pressure, HF heart failure.

quality of the calculated the BP, respectively. However, an adequate comparison is still outstanding.

Evaluation and validation studies

Early studies performed in the 1980s suggested that the PTT can be an indicator of arterial BP [21, 30, 48, 51]. Several studies have been performed in order to evaluate the practicability of this method for continuous BP monitoring. The results and conclusions are partly conflictive. This may be due to different methodological designs of the measurement including the use of different reference methods. The results of representative validation studies for the PTT method are summarized in [Tab. 1](#).

PTT method vs. invasive BP measurements

Invasively measured BP is the gold standard when validating methods of BP measurement. Two studies, which were performed during endotracheal anesthesia in adults and in critically ill infants found unacceptable limits of agreement and low correlations, respectively, for the comparison of intra-arterially measured BP and BP calculated from the PTT [61, 69]. The conclusion of the authors that the pulse wave velocity-based methods may not be accurate enough was also reasonable due to the very low correlations in particular patients [61]. In another study, application of several vasoactive drugs (glyceryl trinitrate, angiotensin II, norepinephrine, salbutamol) induced significant changes of the pre-ejection period in healthy men. The pre-ejection period contributed considerably to the PTT measured as the delay between the R wave of the electrocardiogram and the peripheral pulse wave in this investigation [44]. These results affirm the need of an individual calibration of the system when measuring absolute BP values. Remarkably, the correlation between intra-arterial systolic BP and pulse wave-based pressure was good and the limits of agreement small in a clinical study using ultrasonic Doppler probes [33]. In a recent investigation in normotensive and hypotensive patients, and in patients with cardiac arrhythmias, a one-point calibration of the measuring system of systolic BP relation was applied. Here, differences in the mean val-

ue of BP between the methods were very small. The limits of agreement in the non-hypotensive group were acceptable, while hypotensive subjects and patients with arrhythmias showed clearly greater differences between the methods [7].

PTT method vs. cuff-based BP measurements

Reviewing studies, which compared the PTT method with cuff-based measurements revealed partly conflicting results: A correlation analysis between PTT and instantaneous BP measured by the vascular unloading method led to authors' conclusion that PTT is not an index of BP, although correlations between BP values of the methods were frequently significant under several experimental conditions in this study [51]. Applying the vascular transit time, a measure which excludes the pre-ejection period, Foo et al. [17] found good correlations especially between systolic BP and this measure. Some other investigations suggest the usefulness of the PTT for BP determination. They demonstrated a good association between the variability in BP and the PTT (including the pre-ejection period) and found a good accuracy of BP monitoring based on PTT during exercise [31, 34]. Furthermore, good compliance was observed between the BP, which was continuously measured by cuff-based methods and the PTT during treadmill exercise [56, 62]. Investigation of the repeatability of the PTT method showed reasonable results within 6 months [64].

Recently, several studies have been published in which a one-point calibration was applied. They demonstrated good correlations of the systolic BP determined by the PTT and by cuff-based methods. Also, the limits of agreement were in acceptable ranges in these studies. Based on a non-linear function between pulse wave velocity and systolic BP, the overall correlation factor was 0.83 and limits of agreement were ± 19.8 mmHg in 50 subjects, who exercised on a bicycle ergometer to vary BP [22]. Using the same non-linear function between BP and pulse wave velocity, this group showed very good agreement in the detection rate and the apnea-related changes of the systolic BP [23]. In both studies, differences in systolic BP measured by PTT and cuff-based methods were negligible when

comparing mean values of the measurements. This suggests that the one-point calibration of the PTT method is sufficient for monitoring mean absolute systolic BP. Furthermore, systolic and diastolic BP detected by using PTT correlated to cuff-based measurements under continuous positive airway pressure treatment. Although the bias increased with higher pressure levels in this study, the mean differences did not exceed 7 mmHg, indicating marginal influences of such manipulation on PTT [53].

Limitations of the method

Determination of BP using the PTT is strongly influenced by the quality of the electrocardiogram and finger plethysmography. There are several reasons for disturbance of electrocardiography signals, which lead to missing or false detection of the R wave: electrical noise, movement artifacts, small R wave, and pathological R waves. In addition, the plethysmographic signal can be disturbed, for example by movements, respiratory events, or other events resulting in changes of the hydrostatic pressure. However, the hydrostatic influence depending on body position changes in a lying position during sleep is low and therefore alterations of the body/hand position during sleep will not result in considerable PTT changes. The influence of artifacts can be estimated from two studies in sleep laboratories: The PTT was not available or measurements had more than 50% artifacts in 15% of the investigations in patients of a cardiological sleep laboratory during positive pressure ventilation [53]. Artifacts in the electrocardiogram or plethysmogram led to exclusion of 7 from 34 patients with sleep apnea in another study [23].

The pre-ejection period is an important determinant of the PTT. The influence ranged between 12 and 35% in a study, where the BP was modulated by application of vasoactive drugs [44]. Also, during short-term physical load, the pre-ejection period dominated the PTT in another study [40]. This suggests the use of the phonocardiography signal instead of the electrocardiogram. However, acute calibration of the PTT measurement system can partly circumvent this difficulty [7, 22, 23, 53].

Again, structural properties of the vessel (aged or atherosclerotic arteries) and endothelial dysfunction influence the function-

al relation between pulse wave velocity and blood pressure. Therefore, the measurement of absolute values of blood pressure requires calibration of the system.

Diastolic BP correlates significantly less with the PTT in most of the studies [13, 61, 64]. This may limit the application of the PTT for BP determination. On the other hand, changes in diastolic pressure are in general smaller and this may be a reason for the weaker correlations found in the studies.

Application for sleep medicine

Until now, only two validation studies have been published in the field of sleep medicine [23, 53]. They demonstrate encouraging results regarding the application of the pulse transit method in sleep medicine and research. There are not only necessities for a continuous method, which does not disturb sleep, furthermore sleep also gives good measuring conditions for this method, for example by reduced movement artifacts. Advantages for using the method in the sleep laboratory are also the simplicity

of application and the fact that no additional sensors are necessary. Nearly all equipments for sleep investigation offer the electrocardiogram and finger plethysmography.

Conclusion

PTT is in principle suitable for the continuous monitoring of BP. In contrast to the discrete measurement of BP with 24-h BP devices, it allows the assessment of transient changes in BP such as apnea-related PB events. Determination of BP using the PTT is based on the relation between BP and pulse wave velocity. Estimation of absolute BP values requires calibration of the measurement, since pulse wave velocity also depends on structural properties of the vessel wall influencing the elasticity modulus. Recently, a method was introduced with a one-point calibration approach. Validation studies revealed a good ability for recognition of BP changes and showed acceptable limits of agreement for this method. These results are encouraging for further clinical

evaluation of PTT-based BP measurement in larger populations in accordance to the European guidelines on hypertension management [36].

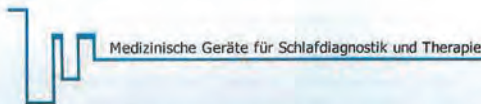
Corresponding address

Prof. Dr. A. Patzak
AG Nierengefäßphysiologie,
Institut für Vegetative Physiologie,
Charité-Universitätsmedizin Berlin
Chariteplatz 1, 10117 Berlin
Germany
andreas.patzak@charite.de

Conflict of interest. On behalf of all authors, the corresponding author states the following: A.H. is employee of Somnomedics GmbH and A.P. advises Somnomedics GmbH in scientific aspects of blood pressure measurement.

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SOMNOmedics GmbH · Am Sonnenstuhl 63 · 97236 Randersacker
Tel: 0931 / 359094-0 · info@somnomedics.de · www.somnomedics.de

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