

## Supplementary file

### Materials and Methods

#### Study design, Setting and Selection of Participants

This prospective cohort study was conducted in the ED of the University Medical Center Groningen during 8 months in 2014. All consecutive patients older than 18 years visiting the ED during work days between 9am and 5pm, in whom (pre)syncope was suspected by the attending physician, were included. The exclusion criteria were not being able to stand for five minutes (min) with minimal assistance, hemodynamic instability (supine systolic BP <90 mmHg), the need for immediate treatment or the presence of a cognitive disorder, if this impaired informed consent. The initial evaluation was performed by the attending physician in the ED. Subsequently continuous noninvasive orthostatic BP measurements were performed by two trained researchers (VvW, DtH). Conclusive information obtained with continuous noninvasive BP measurement was not available during the completion of the evaluation by the attending physician. Additional patient data were derived from the medical records, including the final working diagnosis, determined by the attending ED physician. The protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen and verbal informed consent was obtained from all patients.

#### Continuous noninvasive blood pressure measurement

For continuous measurements Nexfin<sup>®</sup> (BMEYE, Edwards LifeSciences, Irvine, California, USA), a continuous noninvasive Finger Arterial Pressure (FinAP) measurement device was used. FinAP measurement is based on a dynamic (pulsatile) unloading of the finger arterial walls using an inflatable finger cuff with built-in photo-electric plethysmograph. It enables reliable measurement of the arterial pressure waveform at the finger [1-4]. From the finger waveform, heart beats are detected and systolic, diastolic and mean pressure and pulse rate are output in a beat-to-beat mode. FinAP includes a finger cuff and wrist-worn unit containing a fast servo-controlled pressuring system for the continuous adjustment of cuff pressure according to the changes in the plethysmographic output. The finger cuff, a height correction unit, which corrects for movements of the finger when the hand is not kept at heart level, and the wrist-worn unit are connected to a primary unit which holds the air pump, electronics and computer (Figure 1). An important feature of the FinAP is the physioal, a dynamic servo setpoint adjuster, i.e. it defines and maintains the diameter at which the finger artery is clamped. Activation of the physioal procedure is mandatory to maintain accuracy during measurements. At regular time intervals of up to 70 beats the set-point is checked, which gives brief interruptions of the BP recordings. FinAP recordings are similar in appearance to intra-arterial BP recordings, but the measurements are not identical, because arterial waveforms in the finger differ from more central arteries. FinAP has been validated extensively as a reliable method to track orthostatic changes in BP [1-4].

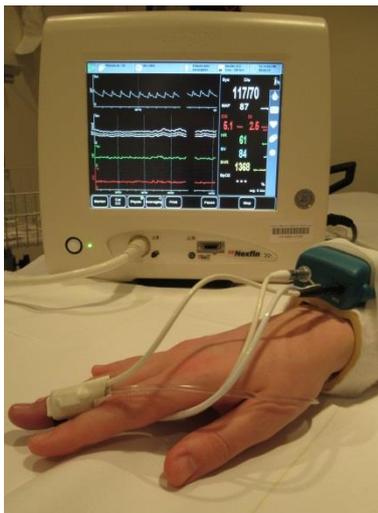


Figure 1. Continuous noninvasive finger arterial blood pressure measurement with Nexfin. Illustrated are the finger cuff and height correction unit connected to the wrist-worn unit.

### **Measurement protocol**

At the start of the orthostatic BP measurement patients were lying in supine position and the Nexfin wrist-worn unit was placed around the wrist and the appropriate cuff size was placed around the middle finger. The height correction unit was connected to the finger cuff and the other part of this unit was placed at heart level. Then the hand with the wrist-worn unit and finger cuff was placed at heart level, supported by a sling, and the height correction unit was zeroed, according to the manufacturer's manual [5]. The automatic physiocal function was activated. Patients were instructed to be silent during the entire measurement and to avoid any movements. After five min of rest in supine position with continuous FinAP registration, the physiocal was disabled, to ensure a continuous BP recording during the active standing up maneuver. Patients were instructed to stand up as quickly as possible, preferably within 3 seconds (s). Elderly patients received assistance if needed. The physiocal was enabled after one min of standing. After five min of standing the FinAP measurement was stopped. Subsequently patients were asked whether they experienced any symptoms during standing, such as light-headedness, dizziness or blurred vision.

### **Data Collection and Processing**

The orthostatic BP measurements with Nexfin were stored on the hard disc of Nexfin for offline analysis. Using Frame Inspector (BMEYE, Amsterdam, The Netherlands) the recordings were converted to Excel files (Excel 2010, Microsoft Office Professional Plus, Microsoft Corp.) for beat-to-beat analysis. These files were used for offline inspection of the quality of the recordings, artifacts and proper position of the marker indicating the start of standing up. Systolic and diastolic BP and heart rate were compared at six time points during orthostasis: baseline (60 s average before standing up), nadir (lowest beat-to-beat systolic BP value within the first 15 s of standing), 30, 60, 120 and 180 s after standing up. For 30, 60, 120 and 180 s a 5-s average was used. The FinAP measurements lasted five min but only the first 180 s were analyzed, according to the consensus definition of orthostatic hypotension [6]. These values were used in the identification of the orthostatic BP recovery patterns. All files were separately analyzed by three investigators (VvW, DtH, MH) and discussed until consensus was reached.

### **Definition of the orthostatic BP recovery patterns**

Defining orthostatic BP recovery patterns follows a recent review that defined normal and abnormal orthostatic BP responses based on small clinical and large epidemiological studies with FinAP measurement [7]. Normal BP recovery was defined as recovery of systolic BP to baseline values at 30 s of standing, not exceeding a decrease of more than 20 mmHg. Initial orthostatic hypotension was defined as a transient decrease of >40 mmHg in systolic BP within 15 s of active standing. Complete BP recovery should be within 30 s of standing. Delayed BP recovery was defined as delayed recovery of systolic BP to baseline values of more than 20 mmHg at 30 s of standing, but not meeting the criteria of classic orthostatic hypotension. Classic orthostatic hypotension was defined as a sustained decrease in systolic BP of  $\geq 20$  mmHg between 60-180 s of standing. With the presence of hypertension (supine systolic BP  $\geq 160$  mmHg) a reduction of  $\geq 30$  mmHg was used. Reflex mediated hypotension was defined as a relative sudden change in autonomic nervous system activity leading to a fall in BP, heart rate and symptoms of cerebral hypoperfusion, which is associated with a heterogeneous group of conditions.

### **References**

- 1 Imholz BP, Wieling W, van Montfrans GA, et al. Fifteen years experience with finger arterial pressure monitoring: assessment of the technology, *Cardiovasc Res* 1998;38:605-16.
- 2 Nowak RM, Sen A, Garcia AJ, et al. Noninvasive continuous or intermittent blood pressure and heart rate patient monitoring in the ED, *Am J Emerg Med* 2011;29:782-9.
- 3 Eeftinck Schattenkerk DW, van Lieshout JJ, van den Meiracker AH, et al. Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff, *Am J Hypertens* 2009;22:378-83.
- 4 Martina JR, Westerhof BE, van Goudoever J, et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin(R), *Anesthesiology* 2012;116:1092-103.
- 5 Anonymous . Nexfin HD Operator's manual 2008; 0086–06.

6 Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome, *Clin Auton Res* 2011;21:69-72.

7 van Wijnen VK, Finucane C, Harms MPM, et al. Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages, *J Intern Med* 2017.