Variability of Peripheral Pulse Wave Velocity in Patients With Diabetes Mellitus Type 2 During Orthostatic Challenge

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Summary

Diabetes mellitus 2 (DM2) is the seventh cause of death worldwide. One of the reasons is late diagnosis of vascular damage. Pulse wave velocity (PWV) has become an independent marker of arterial stiffness and cardiovascular risk. Moreover, the previous studies have shown the importance of beat-to-beat PWV measurement due to its variability among the heart cycle. However, variability of PWV (PWVv) of the whole body hasn't been examined yet. We have studied a group of DM II and heathy volunteers, to investigate the beat-to-beat mean PWV (PWVm) and PWVv in the different body positions. PWV of left lower and upper extremities were measured in DM2 (7 m/8 f, age 68±10 years, BP 158/90±19/9 mm Hg) and healthy controls (5 m/6 f, age 23±2 years, BP 117/76±9/5 mm Hg). Volunteers were lying in the resting position and of head-up-tilt in 45° (HUT) for 6 min. PWVv was evaluated as a mean power spectrum in the frequency bands LF and HF (0.04-0.15 Hz, 0.15-0.5 Hz). Resting PWVm of upper extremity was higher in DM2. HUT increased lower extremity PWVm only in DM2. Extremities PWVm ratio was significantly lower in DM2 during HUT compared to controls. LF and HF PWVv had the same response to HUT. Resting PWVv was higher in DM2. Lower extremity PWVv increased during HUT in both groups. PWVm and PWVv in DM2 differed between extremities and were significantly influenced by postural changes due to hydrostatic pressure. Increased resting PWVm and PWVv in DM2 is a marker of increased arterial stiffness.

Key words

Pulse wave velocity • Variability • Diabetes mellitus • Arterial stiffness • Orthostasis

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Introduction

Pulse wave velocity (PWV) is a gold standard for estimation for the arterial stiffness: lower arterial stiffness leads to the higher PWV. Aortic PWV is an independent predictor of future cardiovascular events and all-cause mortality (Laurent *et al.* 2001, Boutouyrie *et al.* 2002, Vlachopoulos *et al.* 2010, Lee *et al.* 2018). Arterial stiffness evaluated in the form of carotid-femoral or heart-femoral PWV is the most preferred index however both parameters includes mainly central (aortic) PWV (Lee *et al.* 2018). Not only aortic PWV, but also peripheral PWV, such as brachial-ankle or femoral-ankle PWV, can be used as a parameter of vascular damage (Lee *et al.* 2018, McEniery *et al.* 2005, Meyer *et al.* 2016).

PWV depends on the vessel structure and condition. Physiologically, peripheral (muscular) arteries contain smooth muscle layer controlled by the sympathetic nervous system as well as vasoactive substances. The changes of the nervous system affect the compliance of arterial wall (Scott *et al.* 2001 Polónia *et al.* 2003). Aortic compliance is higher than in peripheral arteries compliance due to structural and

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functional differences. Therefore, PWV in peripheral arteries could provide different and more complex information than aortic PWV (Meyer *et al.* 2016).

Other factors influencing PWV are endothelial function, blood pressure, blood volume, arterial distension, and structural changes. PWV is a marker of vascular aging and endothelial function (Lee *et al.* 2018, McEniery *et al.* 2006, McEniery *et al.* 2005). Blood pressure and blood volume are parameters strongly influencing PWV: increased blood pressure and filling of artery lead to arterial distension and as a consequence in a decreasing of compliance (Boutouyrie *et al.* 2002, Moudr *et al.* 2014). The previous studies has shown that Aortic stiffness clearly increases with structural changes caused by age (McEniery *et al.* 2005, Wen *et al.* 2015). In summary, PWV is influenced by many factors associated with vascular function.

Standard measurement of PWV is evaluated as a mean value from several cardiac cycles, mostly supine position. However, most pathological changes can appear only after some provocation or by stress testing such as exercise, position change, or application of vasoactive drugs (Polónia *et al.* 2003, Langer *et al.* 2018, Matejkova *et al.* 2014, Gaddum *et al.* 2014, Obata *et al.* 2016). Conversely, spontaneous variability of PWV without any provocation during steady-state conditions could contain information about the vascular regulatory mechanism. This applies especially to the muscular arteries with variable tone controlled by the autonomic nervous system (ANS) (Joannides *et al.* 1995, Boutouyrie *et al.* 1994). Unlike well-studied variability of beat-to-beat heart rate (HRV) and blood pressure (BPV) used as a marker of the ANS activity the variability of PWV (PWVv) is not fully studied. (Rajendra *et al.* 2006, Honzikova *et al.* 1975, Parati *et al.* 1995). We assume, that PWV variability expressed by spectral analysis contains similar spectral components like in HRV and BPV because of the interaction between heart rate, blood pressure, and PWV (Svacinova *et al.* 2015).

Diabetes mellitus type 2 as a chronic progressive vascular disease (DM2) affects PWV by several ways. Endothelial dysfunction and structural arterial changes are caused by long-lasting hyperglycemia and hyperinsulinemia. Diabetic autonomic neuropathy impairs sympatho-vagal balance toward sympathetic predominance over the muscular arteries (Cruickshank *et al.* 2002). DM2 is also accompanied by hypertension, atherosclerotic process, and associated complications.

We have studied a group of mid age DM II and young heathy volunteers, to investigate the differences in mean PWV (PWVm) and PWVv. Both groups were measured at the tilting table.

To provoke the shift in the variability of PWV influenced by age and DM2.

The aim of the preliminary study was to analyze the effect of the orthostatic challenge to the lower and upper extremities PWV and its variability in DM2 and health control volunteers.

Methods

Subjects

Studied group contained 15 patients with DM2 (7 male/8 female, age 68±10 years, blood pressure 158/90±19/9 mm Hg). DM2 volunteers without other serious comorbidities was an only inclusion criterion. Control group consisted of 11 healthy young volunteers (5 male/6 female, age 23±2 years, blood pressure 117/76±9/5 mm Hg). The main exclusion criteria for healthy control group were acute infection, cardiovascular diseases, obesity, diabetes mellitus, and ingestion of substances affecting the cardiovascular system at least 24 h before measurement.

Pulse wave velocity recording

Multichannel bioimpedance monitor (MBM, developed by the Institute of Scientific Instruments of The Czech Academy of Sciences) is the continuous beat to beat measurement of the elasticity of arteries (Plesinger *et al.* 2014, Matejkova *et al.* 2015, Vondra *et al.* 2016, Langer *et al.* 2018, Soukup *et al.* 2019). The method is based on the bioimpedance principle. Basically, transient blood flow increase caused by pulse wave passing between two electrodes induces impedance change. PWV can be evaluated from distances between electrodes and durations of pulse wave passage. Simultaneously electrocardiogram (ECG) was recorded. This method is able to evaluate beat-to-beat PWV in various body parts separately (Fig. 1). In this study, sequences of PWVs were recorded in the left arm and left leg.

Protocol

The participants were lying in the supine position resting 6 min before performing the measurement. Then the PWVs were measured for the 6 min (phase of supine position). After measurement at the supine position participant was tilted at the neurological tilting table at the degree of 45° for the 6 min (phase HUT). Current electrodes were placed at the neck, hands,

and legs. Bioimpedance electrodes were placed at the chest, hands, and legs for obtaining limb PWV at the two different hemodynamical conditions.

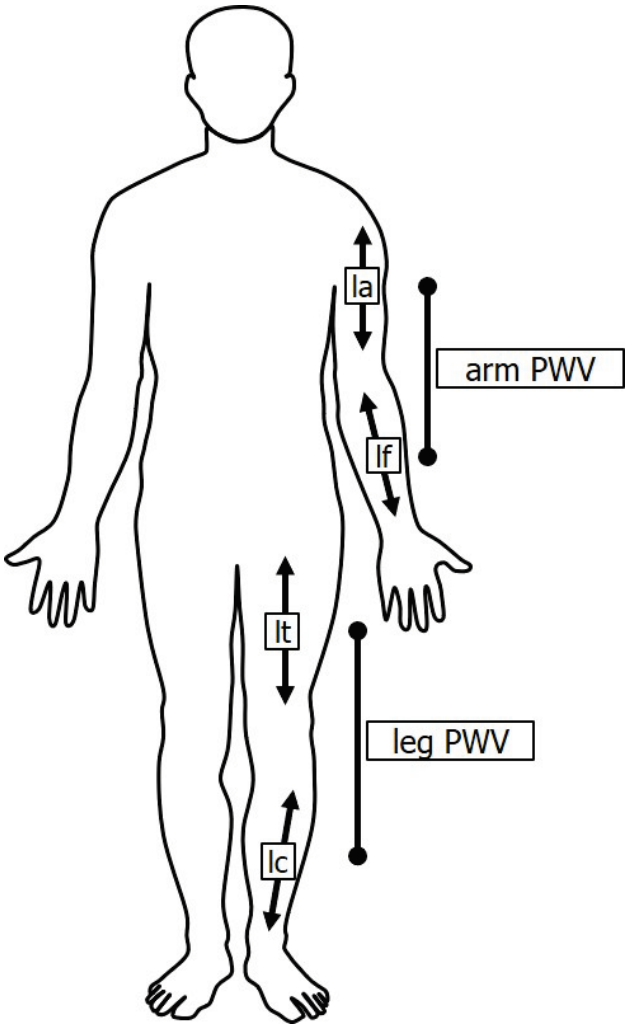

Fig. 1. Multichannel bioimpedance method: arrows indicate the position of electrodes (a total of 8 electrodes, 4 for each extremity), where Ia stands for arm bioimpedance lead, If – forearm bioimpedance lead, It – thigh bioimpedance lead and Ic – calf bioimpedance lead. Passage of the pulse wave between the electrodes determining the lead causes impedance change. PWV is calculated from distance between physical midpoints of the leads Ia and If, respectively It and Ic and transit time of the pulse wave.

Data analysis

Mean PWVs were evaluated from sequence *pwv* containing 300 consecutive beat-to-beat PWV samples. Mean arm and leg PWV (PWVm) were evaluated for each subject and phase. The ratio of the arm/leg PWVm was calculated for each subject and phase of measurement. Variability of the beat-to-beat PWV (PWVv) was evaluated as a mean spectral power of *pwv* in the low-frequency band (LF, 0.04-0.15 Hz) and high-frequency band (HF, 0.15-0.5 Hz). Kolmogorov-Smirnov test proved non-Gaussian distribution of data; therefore, non-parametric tests were used. Mann-Whitney test was used for the evaluation of the difference between DM2 patients and controls. Wilcoxon pair test was used for evaluation of the difference between phases and extremities.

Results

Example of beat-to-beat PWV for one DM2 patient and control is shown in Figure 2. Supine PWVm was higher in DM2 than in controls (Fig. 3). HUT led to increase of leg PWV in DM2. PWVm ratio arm/leg significantly decreased during HUT in DM2 compared to controls, therefore HUT PWVm ratio arm/leg was lower in DM2 in comparison to controls.

PWVv is shown in Figure 4. HUT led to a significant increase in PWVv in controls regardless to the frequency band or extremity. DM2 showed an increase of PWVv only in the leg. However, variability in DM2 was higher in the leg than in arm during HUT in both frequency bands. DM2 had higher PWVv than controls in the following variables and situations: arm-supine-LF, arm-supine-HF, leg-supine-HF, arm-hut-HF.

Discussion

Innovative method of bioimpedance PWV measurement used in this study has several advantages. It can detect beat-to-beat PWV in various parts of the body. Therefore not only mean PWV but also changes of PWV in response to the orthostatic challenge in particular arteries could be analysed in this study (Plesinger *et al.* 2014, Plesinger *et al.* 2014, Vondra *et al.* 2016). This study was focused on changes of PWV and its variability in the group of healthy participants and DM2 patients, to evaluate the variables reflecting the changes in the vessels. Participants from the healthy control were selected from a younger age to exclude the other vascular pathologies.

Changes of mean PWV

Supine PWV was higher in DM2 than in controls. HUT led to the highlighting of the difference between DM2 and controls in the leg. DM2 had a stronger response to the HUT, especially in leg, which was expressed by arm/leg ratio.

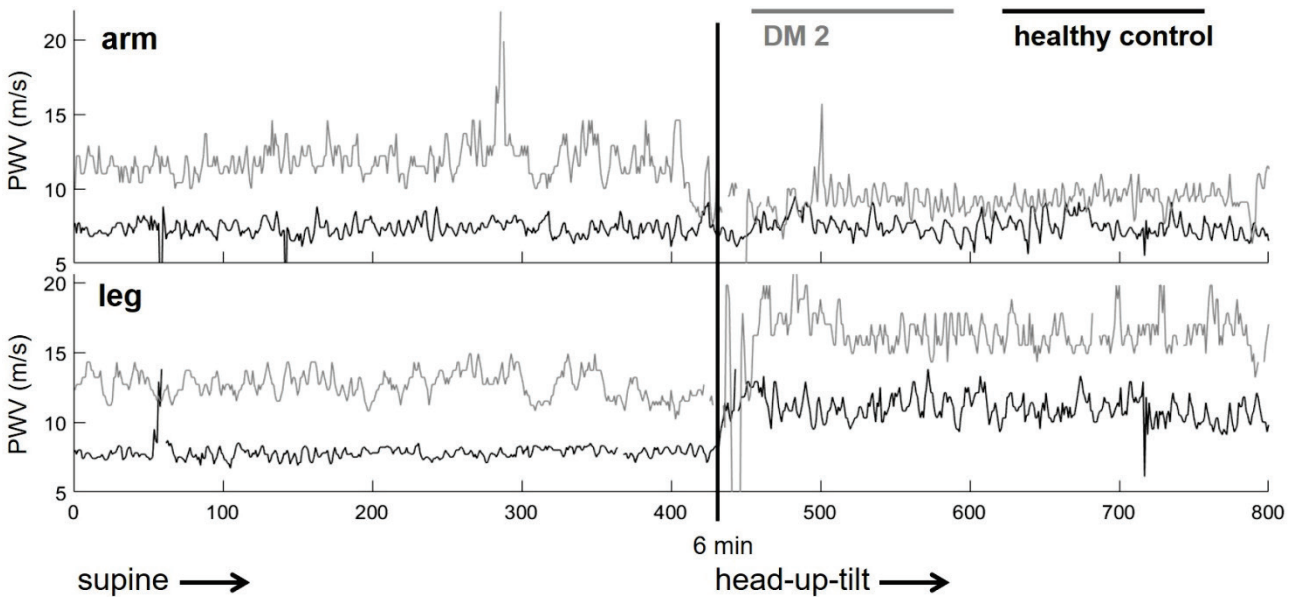

Fig. 2. An example of beat-to-beat PWV in leg and arm in patient with diabetes mellitus 2 (DM2) and healthy control. Tilt-table test was made in 45°.

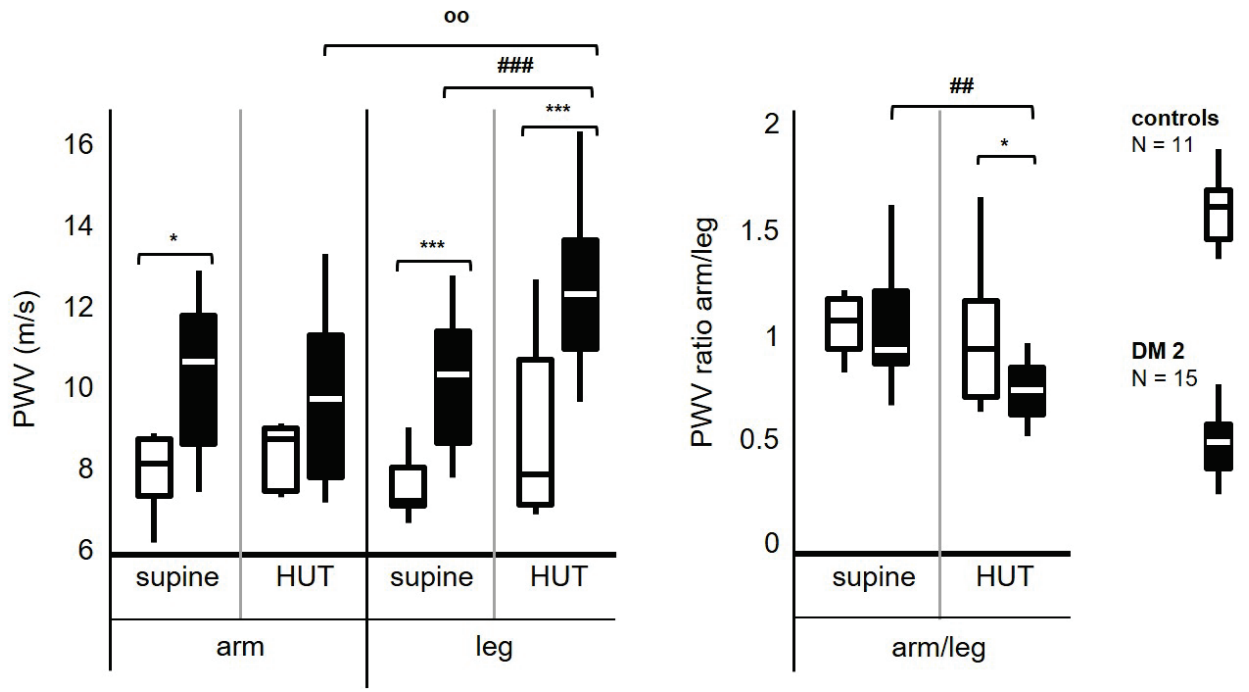

Fig. 3. Distribution of PWV and ratio PWV arm/leg. Subjects: 11 healthy controls: (5 male/6 female) and 15 patients with diabetes mellitus 2 (DM2, 7 male/8 female). HUT: head-up-tilt in 45°. DM2 vs. controls (Mann-Whitney test): * p<0.05; ** p<0.01; *** p<0.001. Supine vs. HUT (Wilcoxon test): # p<0.05; ## p<0.01; ### p<0.001. PWV arm vs. PWV leg (Wilcoxon test): ° p<0.05; °° p<0.01.

Blood pressure is a very important determinant of PWV regardless of the structural and functional arterial wall changes (Wang *et al.* 2014). Both, diabetes mellitus 2 and higher age, increase PWV by increased blood pressure (Kim *et al.* 2006, Wen *et al.* 2015). Increase of the leg PWV during the orthostatic challenge was clearly caused by blood redistribution and increased hydrostatic pressure and volume in lower limbs (Plesinger *et al.* 2014, Matejkova *et al.* 2015). Arterial compliance determining PWV is not constant. Compliance non-linearly depends on arterial distension caused by increased transmural pressure and/or on filling of the artery (Moudr *et al.* 2014, Cymberknop *et al.* 2019, Weltman *et al.* 1964).

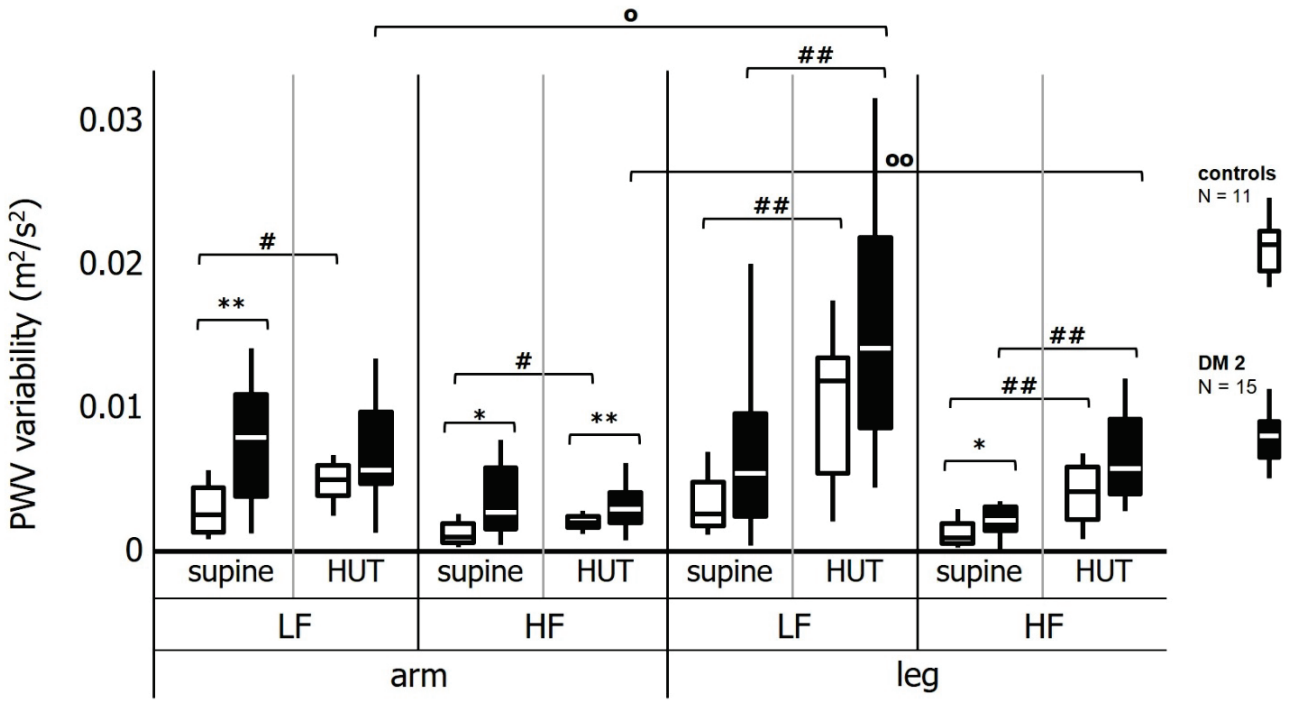

Fig. 4. Distribution of PWV variability evaluated as a spectral power in low frequency (LF: 0.04-0.15 Hz) and high frequency band (HF: 0.15-0.5 Hz). Subjects: 11 healthy controls: (5 male/6 female) and 15 patients with diabetes mellitus 2 (DM2, 7 male/8 female). HUT: head-up-tilt in 45°. DM2 vs. controls (Mann-Whitney test): * $p<0.05$; ** $p<0.01$. Supine vs. head-up-tilt 45° (Wilcoxon test): # $p<0.05$; ## $p<0.01$; PWV arm vs. PWV leg (Wilcoxon test): ° $p<0.05$; °° $p<0.01$.

We supposed that DM2 patients had negatively influenced endothelial function and led to the structural changes of the arterial wall, both increasing arterial stiffness (McEniery *et al.* 2006). Higher blood pressure or remodeled arterial wall could be a possible reason for higher resting PWV in DM2. Increased arterial stiffness in diabetes mellitus 2 was proved in elastic (aortic) as well as in peripheral (muscular) arteries of diabetics (Zhang *et al.* 2011).

DM2 showed a stronger increase of leg PWV compared to controls. It could be given by changed autonomic control over the vessels and dysregulation of blood redistribution, diabetic neuropathy and angiopathy (Chorepsima *et al.* 2017). Moreover, vascular response (vasoconstriction/increasing of the vascular tone) to the orthostatic challenge in lower limbs is provided by the local mechanism such as veno-arteriolar response (VAR) (Brothers *et al* 2009). In case of vascular impairment in DM2 the primary target is microcirculation and as the result affection of VAR (Strain and Paldánius 2018, Namgoong *et al.* 2019). The orthostatic challenge can be a useful provocation maneuver to better detect pathology in vascular response, but correction of PWV on blood pressure in the measured artery is strongly recommended.

Changes of PWV variability

Changes of PWV variability were more complex. DM2 generally had higher resting PWVv than controls. HUT led to increase of PWVv in the legs of both groups, while variability in arm increased only in controls. During HUT, DM2 had higher PWVv in the leg than in the arm.

Studies analyzing PWV variability were usually focused on day-to-day or longer intervals between measurements mainly to evaluate the reproducibility of PWV (Tripkovic *et al.* 2014, Kallem *et al.* 2013, Bode *et al.* 2012). Beat-to-beat PWV variability is practically unexplored, but some studies described variability in differences between peripherally measured pulse intervals and RR-intervals from ECG, which are associated with the similar source of variability as a PWV (Hayano *et al.* 2005, Schäfer and Vagedes 2013, Del Paso *et al.* 2010).

Wang *et al.* (2014) proved that transit time, as a component of a PWV (PWV = distance / transit time) together with heart rate can be used to calculate blood pressure. Therefore transit time can be taken as a surrogate for BPV.

BPV and HRV expressed by spectral analysis contains well known spectral components in LF and HF band, therefore we expected at least some similarities in power spectra of PWV (Honzikova *et al.* 1975, Parati

et al. 1995). We observed higher PWVv in LF, but the response of LF and HF to HUT did not differ.

Higher variability in LF was probably connected with low-frequency BPV called Mayer waves. It is a question if the variability in PWV was given mostly by BPV, or PWV variability and BPV were of the same origin, i.e. slow changes of the vascular tone. Orthostatic challenge leads to the Mayer waves formation and increases of BPV in LF (Julien 2006, Myers *et al.* 2001). The increase is associated with the activation of the sympathetic nervous system. Therefore, the connection with the Mayer waves can be supported by finding, that LF PWVv markedly increased during HUT. LF BPV increase during hut is presented also in diabetes mellitus 2 without neuropathy. Diabetic neuropathy lead to lower LF BPV during orthostatic challenge (Casali *et al.* 2018, Wang *et al*. 2011).

Higher PWV variability in DM2 compared to controls could be explained by other hypotheses. Firstly, it was given by increased arterial stiffness and worsened ability of arteries to dump fast BP changes compared to controls. It is possible, that impaired autonomic control over the arteries in DM2 caused higher changes of vascular tone (Verrotti *et al.* 2014). And finally, generally higher mean PWV provided larger space for PWVv.

Conclusions

Multichannel bioimpedance PWV is a beat-to-beat non-invasive measurement of the PWV with the possible simultaneous examination legs and arms. Mean PWV in lower and upper limbs responded differently to the HUT because of higher hydrostatic pressure in lower limbs. The resting PWV was higher in DM2, but HUT led to highlighting the difference in lower limbs. PWV ratio arm/leg seems to be interesting variable for clinical implementation and evaluation of arterial stiffness in people at higher cardiovascular risk. BPV is probable source for PWVv. Resting PWVv was higher in DM2 as well. Although HUT led to the increase of PWVv especially in lower limbs, the difference between healthy controls and DM2 during HUT was not significant. LF PWVv variability during HUT could be associated with Mayer waves in BPV. PWVv is a complex parameter and there are many possible reasons for higher mean PWV and its variability in DM2, such as diabetic neuropathy and changed sympathetic response to the HUT, vascular remodelation, endothelial dysfunction or other. PWVv probably contains complex information about all these factors, which requires further investigation.

Limitations

The influence of aging, diabetes mellitus and hypertension on PWV and its variability cannot be separated. Therefore, the major limitation of the study is in the selection of the control group, when we have investigated the healthy group of young adults. As a control group, normotensive age-matched non-diabetics should be used. However, the aim was to prove, how impedance is able to detect these clear changes in arterial stiffness. For a better understanding of PWV changes, correlation with diabetic parameters such as duration of diabetes, glucose tolerance, fasting plasma glucose, glycated hemoglobin, etc. should be made (Chorepsima *et al.* 2017, Zhang *et al.* 2011).

Conflict of Interest

There is no conflict of interest.

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