Preejection Period as a Sympathetic Activity Index: a Role of Confounding Factors

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Summary

In previous studies, one of the systolic time intervals – preejection period (PEP) – was used as an index of sympathetic activity reflecting the cardiac contractility. However, PEP could be also influenced by several other cardiovascular variables including preload, afterload and diastolic blood pressure (DBP). The aim of this study was to assess the behavior of the PEP together with other potentially confounding cardiovascular system characteristics in healthy humans during mental and orthostatic stress (head-up tilt test – HUT). Forty-nine healthy volunteers (28 females, 21 males, mean age 18.6 years (SD=1.8 years)) participated in the study. We recorded finger arterial blood pressure by volume-clamp method (Finometer Pro, FMS, Netherlands), PEP, thoracic fluid content (TFC) – a measure of preload, and cardiac output (CO) by impedance cardiography (CardioScreen® 2000, Medis, Germany). Systemic vascular resistance (SVR) – a measure of afterload – was calculated as a ratio of mean arterial pressure and CO. We observed that during HUT, an expected decrease in TFC was accompanied by an increase of PEP, an increase of SVR and no significant change in DBP. During mental stress, we observed a decrease of PEP and an increase of TFC, SVR and DBP. Correlating a change in assessed measures (delta values) between mental stress and previous supine rest, we found that ΔPEP correlated negatively with ΔCO and positively with ΔSVR. In orthostasis, no significant correlation between ΔPEP and ΔDBP, ΔTFC, ΔCO, ΔMBP or ΔSVR was found. We conclude that despite an expected increase of sympathetic activity during both challenges, PEP behaved differently indicating an effect of other confounding factors. To interpret PEP values properly, we recommend simultaneously to measure other variables influencing this cardiovascular measure.

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Introduction

Preejection period (PEP) belongs to three basic systolic time intervals (together with left ventricular ejection time – LVET and total electromechanical systole duration – QS_2). PEP is significantly affected by the heart inotropy and is commonly regarded as an index of cardiac sympathetic (β-adrenergic) activity (Larkin and Kasprowicz 1986, Cacioppo *et al.* 1994a, Schächinger *et al.* 2001, Parry *et al.* 2015). PEP is the sum of the electromechanical delay (from the Q wave on electrocardiogram to the onset of pressure rise in the left ventricle) and the duration of the isovolumic contraction (rapid rise of the left ventricular pressure up to the level of the diastolic aortic pressure, when aortic valve opens – Fig. 1). While the electromechanical delay in healthy human takes 30 – 40 msec and is only minimally affected by different physiological and pathophysiological states (Lewis *et al.* 1977, Afonso *et al.* 2009), the duration

of isometric contraction is more variable. The duration of the isometric contraction phase dominantly influencing the duration of PEP is considered to depend primarily on cardiac contractility but it is also significantly influenced by cardiac preload (Lewis *et al.* 1977, Buch *et al.* 1980, Cacioppo *et al.* 1994a, Beauchaine *et al.* 2013) and afterload (Hodges *et al.* 2010). An increase in cardiac preload leads to increased contraction strength *via* Frank-Starling mechanism and subsequently to a decrease of PEP. In contrast, increased systemic vascular resistance prolongs the PEP by increased cardiac afterload (Sherwood *et al.* 1990). Additionally, changes in diastolic blood pressure (DBP) could also have an impact on the duration of the PEP (Fig. 1) (Lewis *et al.* 1974). Taken together, when using PEP as an index of cardiac sympathetic activity influencing ventricular contractility it is important to consider preload, afterload and DBP as potential confounding factors (Fig. 1).
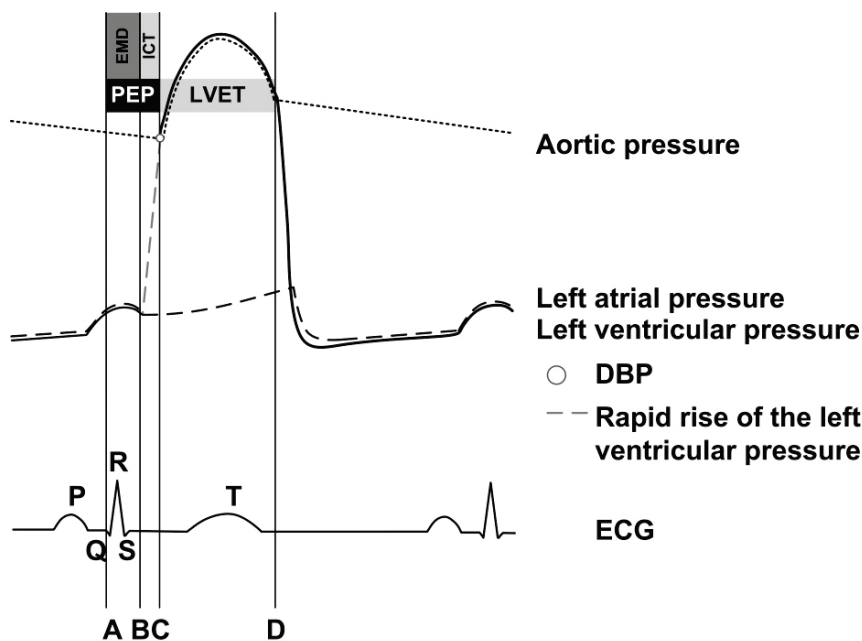

Fig. 1. Components of the PEP (Katz 2011). Theoretically, when diastolic blood pressure (DBP) increases, the aortic valve opening (point C) is reached later and PEP could be prolonged. EMD denotes the electromechanical delay (A-B), ICT denotes isovolumic contraction time (B-C); A, B, C and D denote Q wave onset, closing of the mitral valve, opening of the aortic valve, and closing of the aortic valve, respectively.

In previous studies the PEP was used as an index of sympathetic activity during different states and in different study groups. Although the influence of confounding factors on PEP is assumed, the behavior of the confounding factors (preload, afterload and DBP) together with PEP during various physiological conditions in healthy subjects was only rarely studied.

Therefore, the aim of this study was to assess the changes of the PEP together with other cardiovascular system characteristics during mental and orthostatic stress in healthy humans.

Methods

Subjects

In total, 49 healthy volunteers (28 females, 21 males) with a mean age of 18.6 years (SD=1.8 year, range 15.8 – 22.6 years) participated in this study. Subjects were instructed not to use substances influencing autonomic nervous system or cardiovascular system activity. Female subjects were examined in the proliferative phase of the menstrual cycle. All procedures were approved by Ethical Committee of the Jessenius Faculty of Medicine, Comenius University and all participants signed a written informed consent.

Data acquisition

We recorded finger arterial blood pressure (DBP and mean arterial pressure (MBP)) by volume-clamp method (Finometer Pro, FMS, Netherlands). We used reconstructed brachial arterial pressure applying return-to-flow calibration to improve the accuracy of blood pressure measurement. MBP was calculated as the true integrated mean pressure between the current and the next upstroke and DBP as the low pressure just before the current upstroke. The PEP, thoracic fluid content (TFC) – a measure of preload, and cardiac output (CO) were recorded by impedance cardiography (CardioScreen® 2000, Medis, Germany). Systemic vascular resistance (SVR) – a measure of afterload – was calculated as a ratio

of mean arterial pressure and CO, assuming zero venous pressure at the right atrium (Krzesiński *et al.* 2012, Krzesiński *et al.* 2016, Lasater and Von Rueden 2003, Sodolski and Kutarski 2007, Xiajuan *et al.* 2013). The duration of the PEP was defined as the time interval between R peak of the ECG and the B point of dZ/dt of the ICG and TFC was calculated from the base impedance Z_0 (TFC=1,000/Z_0).

Study protocol

During the whole measurement, the volunteers were asked to avoid disturbing movements and speaking. They were positioned on the tilt table with the feet in contact with the footboard at the end of the table and restraining strap was secured at the thigh level to provide subject support and safety. The study protocol consisted of four phases: supine rest (15 min), head-up tilt (HUT, the subject was tilted to 45 degrees on the motor driven tilt table for 8 min to evoke mild orthostatic stress), supine recovery (10 min), followed by mental arithmetic task (MA) in the supine position for 6 min. During the MA task the subject was instructed to sum up three-digit numbers (until one-digit number was reached) displayed on the ceiling of the examination room by a data projector. After deciding if the final one-digit number was odd or even, the subject had to click by computer mouse on the corresponding push button projected on the ceiling. During the mental arithmetic task, the subject was disturbed by the rhythmic sound of a metronome and instructed to perform the mental arithmetic task as quickly as possible with a minimal error rate.

Data analysis

To avoid transient changes, we have extracted following 300 beats lasting segments from the original recordings for data analysis: for the first phase the analysed segment started 8 min after the beginning of this phase, for the second phase 3 min after the change of the position, for the third phase 7 min before starting the MA task and for the fourth phase 2 min after starting of this phase. We have calculated median values of beat-to-beat recorded cardiovascular measures (PEP, TFC, SVR, and DBP) for each phase. As the next step, the change in median values (delta values: ΔPEP, ΔTFC, ΔSVR and ΔDBP) as a response to HUT (a change from phase 1 to phase 2: median value from phase 2 minus median value from phase 1) and as a response to MA (a change from phase 3 to phase 4: median value from phase 4 minus median value from phase 3) were calculated.

Statistical analysis

Due to non-normal distribution of the assessed variables, nonparametric tests were used for statistical analysis. A comparison between median values (median PEP, TFC, SVR and DBP) obtained from different phases (phase 2 vs. 1 and phase 4 vs. 3) was performed by Wilcoxon signed-rank test. The correlations between ΔPEP and ΔTFC, ΔSVR, ΔDBP, were calculated separately for HUT and MA using Spearman correlation analysis. The results were considered statistically significant at P<0.05. The statistical analysis was performed using statistical software SYSTAT 13 (Systat Software Inc., USA).

Results

Response to orthostasis

While PEP and SVR during HUT were significantly higher than during supine rest (for both P<0.0001), TFC, MBP and CO were significantly lower compared to preceding supine rest phase (P<0.0001 for each). No significant change in DBP was observed during HUT compared to previous phase (P=0.5343). Correlating a change in analyzed measures (delta values) between HUT and previous supine rest we found no significant correlation between ΔPEP and ΔTFC (rho=-0.027, P=0.854), ΔSVR (rho=0.212, P=0.143), ΔDBP (rho=0.003, P=0.984), ΔMBP (rho=-0.143, P=0.327) or ΔCO (rho=-0.216, P=0.136) (Fig. 2, 3).

Response to mental stress

PEP significantly decreased compared to preceding supine recovery during MA (P=0.0025), whileas TFC, SVR, MBP, DBP and CO significantly increased (P≤0.0022). Analyzing the correlations between responses to mental task, we found a significant negative correlation between ΔPEP and ΔCO (rho=-0.526, P=0.0001) and a significant positive correlation between ΔPEP and ΔSVR (rho=0.333, P=0.019). No significant correlation between ΔPEP and ΔTFC (rho=0.115, P=0.432), ΔDBP (rho=-0.126, P=0.387) or ΔMBP (rho=-0.242, P=0.094) was found.

Discussion

Despite an expected increase in cardiac sympathetic activity during both orthostatic test and cognitive load associated with mental arithmetics task, the changes in PEP were unequivocal: PEP increased

during HUT but it decreased during MA. Our analysis revealed the important influence of other mechanisms on the PEP duration that should be taken into consideration when PEP is analysed and interpreted.
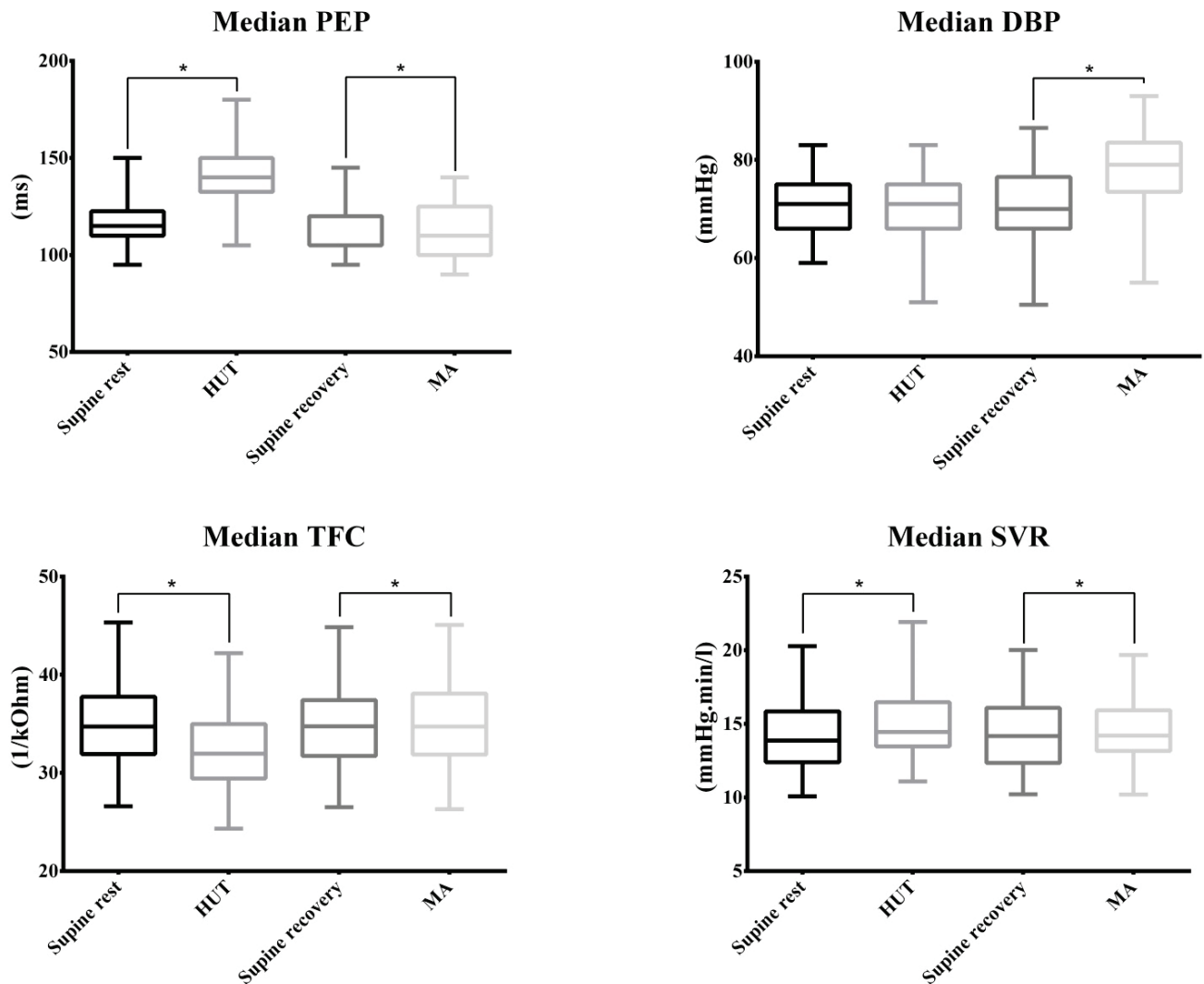

Fig. 2. Median values of PEP, DBP, TFC and SVR during four phases of study protocol. * denotes significant difference, PEP − preejection period, DBP − diastolic blood pressure, TFC − thoracic fluid content, SVR − systemic vascular resistance, HUT − head-up tilt, MA − mental arithmetic.
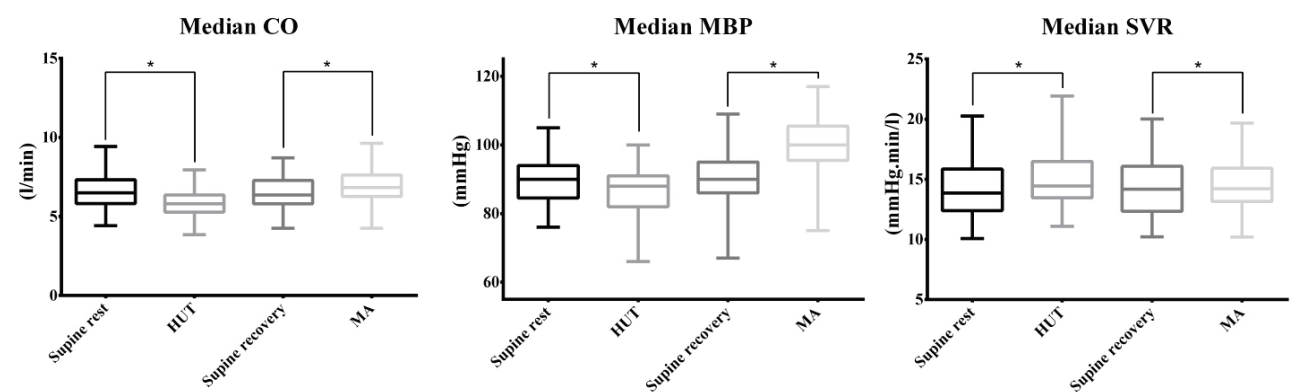

Fig. 3. Median values of CO, MBP, and SVR in four phases of study protocol. * denotes significant difference, CO − cardiac output, MBP − mean arterial pressure, SVR − systemic vascular resistance, HUT − head-up tilt, MA − mental arithmetic.

The cardiac inotropy being importantly influenced by the positive inotropic effect of the sympathetic branch of the autonomic nervous system can significantly influence the duration of PEP. Therefore, PEP has been proposed as a promising index of the cardiac sympathetic activity with a potentially important diagnostic and prognostic information value (Newlin and Levenson 1979). In a series of studies conducted over the last four decades, it was found that the duration of PEP is modified by a variety of physiological and pathological conditions. Factors prolonging the PEP include age, preload reduction, negative inotropic agents, heart failure and left bundle branch block. The shortening, on the other hand, occurs during exercise, emotional stress, as a response to positive inotropic agents, in aortic valve diseases, and acute hypoxemia (Lewis *et al.* 1977, Garrard *et al.* 1970, van Lien *et al.* 2013, Mensah-Brown *et al.* 2010). In the study comparing various sympathetic activity related indexes the PEP overcome the LF/HF ratio from the heart rate variability analysis as an index of the cardiac sympathetic activity (Goedhart *et al.* 2008).

Our study was aimed on the assessment of the PEP changes together with other potentially confounding cardiovascular system characteristics in healthy humans during physical (HUT) and mental (MA) challenges. The major motivation to perform this study was to improve our understanding on the potential limitations to use PEP as an index of cardiac sympathetic activity. There are many studies evaluating the duration of PEP during different physiological (change in the body position from supine to sitting and active or passive orthostasis, cognitive tasks, cold-pressor test, aging, etc.) and pathological (patients with heart failure, hypertension, atrial fibrillation, coronary artery disease, preeclampsia, chronic renal failure, etc.) states together with other measures possibly influencing PEP (Garrard *et al.* 1970, Stafford *et al.* 1970, Carroll *et al.* 1991, Fahrenberg and Foerster 1991, Mezzacappa *et al.* 1999, Kelsey *et al.* 2000, Schächinger *et al.* 2001, Schneider *et al.* 2003, El-Dawlatly *et al.* 2005, Richter *et al.* 2009, Hodges *et al.* 2010, Oben *et al.* 2014, Cieslak *et al.* 2015). However, in only two previous studies (in patients with cardiac failure and in morbidly obese patients) the PEP was measured together with three major confounding cardiovascular variables (preload, afterload, DBP) (Packer *et al.* 2006, El-Dawlatly *et al.* 2005). The study focused on the assessment of the PEP changes during two different stress conditions (physical and cognitive challenge) together with other confounding parameters in healthy subjects is

still missing.

The mechanisms of adaptation to orthostatic stress are well known. During orthostasis – in our study we used a passive orthostasis – HUT – venous pooling of the blood in the lower portion of human body leads to a decrease in cardiac preload causing a decreased ventricular filling (end-diastolic volume), stroke volume and cardiac output. An increased afterload due to peripheral vasoconstriction was also found during orthostatic challenge (Stafford *et al.* 1970, Chan *et al.* 2007, Cacioppo *et al.* 1994b, Bettencourt *et al.* 2008, Svacinova *et al.* 2015). During HUT, we observed a significant increase in PEP duration, together with a decreased cardiac preload (a decrease in TFC from ICG), increased SVR and only negligible change in DBP. The prolonged PEP as a response to HUT was consistently found in previous studies despite the assumed increase of the sympathetic activity to the heart (Chan *et al.* 2007, Lewis *et al.* 1977, Ovadia *et al.* 1995). Considering the observed increase in PEP during HUT in the context of other cardiovascular characteristics changes, a decreased preload (TFC) evoked either by orthostatic maneuver itself or related to the concomitant tachycardia (a decrease of preload associated with a shorter duration of diastole) and an increased afterload (SVR) should be taken into consideration. The decreased preload leads to a prolongation of PEP *via* a decreased strength of cardiac contraction mediated by Frank-Starling mechanism (a decrease in end-diastolic volume results in a decrease of the contraction strength). We assume that the contribution of both preload and afterload varies among individuals and therefore we did not found statistically significant correlations between a change in PEP (ΔPEP) and ΔTFC or ΔSVR related to orthostasis in the whole analyzed group. The decreased strength of ventricular contraction (expressed also by a decreased MBP) together with an increased SVR (peripheral vasocontriction) leads to a decreased CO potentially resulting in an orthostatic syncope in susceptible persons, if compensatory mechanisms fail (Critchley *et al.* 1997, Brignole *et al.* 2001, Kanjwal *et al.* 2015).

During cognitive tasks, several more or less expressed changes occur: parasympathetic activity decrease and/or a sympathetic activity increase cause an increased heart rate (positive chronotropic effect), stronger contractions of the heart muscle (positive inotropic effect), vasoconstriction in the renal and splanchnic circulations and vasodilatation in skeletal

muscles (Lindvall *et al.* 1991, Kuipers *et al.* 2008, Widjaja *et al.* 2015). Mental load in our study evoked by mental arithmetics changed SVR only mildly – a mild but significant increase in SVR could be attributed to the predominance of sympathetic nervous system mediated vasoconstriction in our study. Blood redistribution could be also responsible for a slight increase in TFC. Theoretically, an increase in SVR could itself lead to an increase in PEP, because higher afterload will prolongate preejection period by prolonging time needed to open the aortic valve without changes in contractility (Houtveen *et*

al. 2005). However, in our study during MA an increase of SVR was associated with a decrease in PEP duration both reflecting an increase in sympathetic activity towards vasculature and heart. As can be seen from the positive correlation illustrated on Figure 4, in subjects with more expressed vasoconstriction (higher ΔSVR), a decrease in PEP (ΔPEP) is not as prominent as in subjects in whom ΔSVR was close to zero. We suggest that an expected decrease in PEP associated with sympathetic stimulation could be opposed by a concomitant increase in SVR.
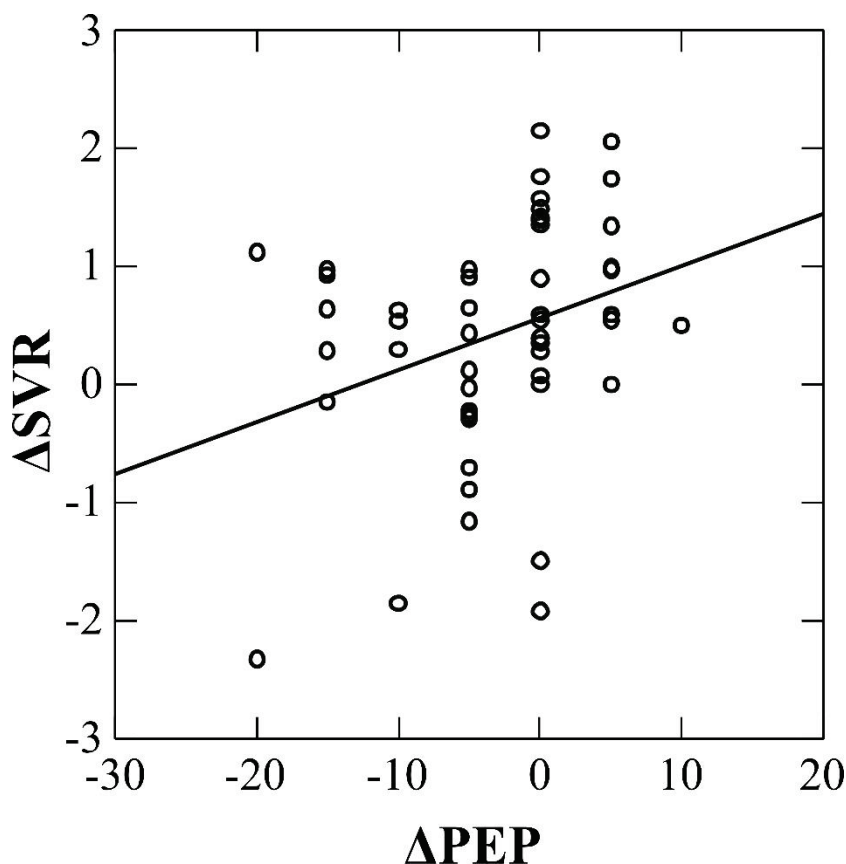

Fig. 4. Scatterplot between a change in preejection period (ΔPEP) and ΔSVR (a change in systemic vascular resistance). Each circle corresponds to one subject. In subjects with more expressed vasoconstriction (higher ΔSVR), a decrease in PEP (ΔPEP) is not as prominent as in subjects in whom ΔSVR was close to zero.

An increased contractility expressed by a decreased PEP during MA is significantly correlated with an increase of cardiac output – this finding illustrates the involvement of the positive inotropic effect of sympathetic component of autonomic nervous system in an increase of CO during cognitive load. As can be seen from the scatterplot (Fig. 5), in subjects with less expressed decrease in PEP (with ΔPEP≥0), the CO increase was less expressed.

The shortening of PEP during mental stress was also found in previous studies (Harrell and Clark 1985, Carroll *et al.* 1991, Berntson *et al.* 1994, Kelsey *et al.* 2000, Schneider *et al.* 2003). Alternatively, a slightly but

significantly increased preload (an increased TFC) could lead to a decrease of PEP observed during MA. However, this possible mechanism is not supported by a significant correlation between ΔPEP and ΔTFC.

Study limitations

Our results and conclusions are based on the measurement of cardiovascular parameters by non-invasive methods potentially introducing a measurement error in our analysis. Our results can be influenced by the measurement error introduced by the non-invasive blood pressure measurement using photoplethysmographic volume clamp method. Validation studies conclude that

although the absolute values of finger blood pressure can be distorted, the changes in the blood pressure can be measured with a good precision (Bogert and van Lieshout 2005, Imholz *et al.* 1998). To minimize the error in

absolute values of blood pressure and to improve the accuracy of its measurement, reconstructed brachial arterial pressure using the return-to-flow calibration was applied in our study.
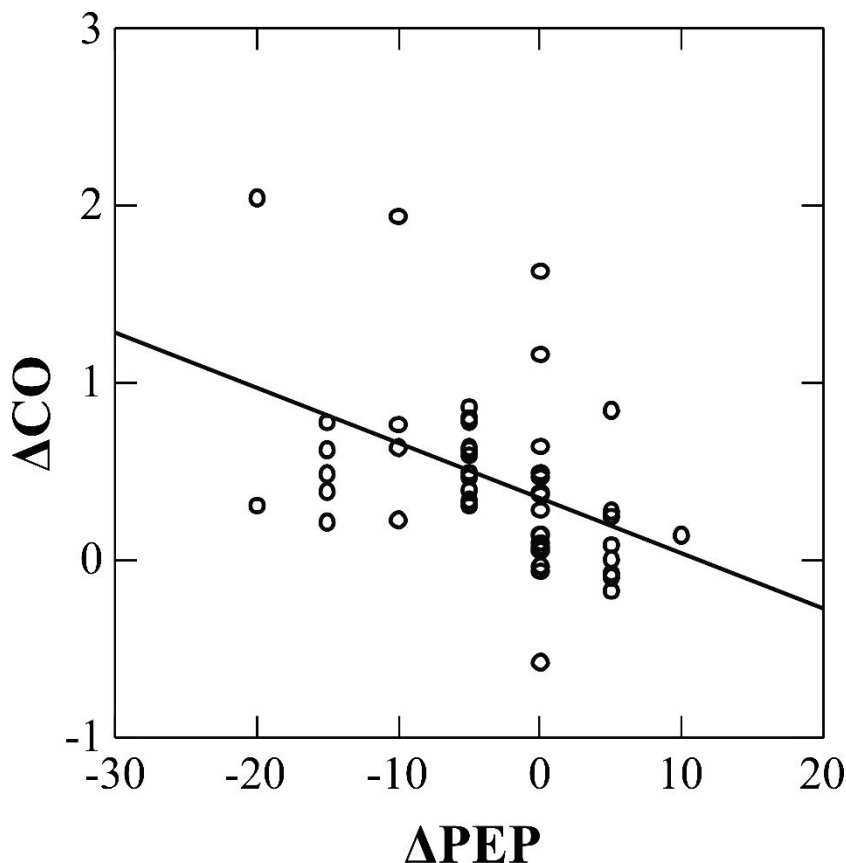

Fig. 5. Scatterplot between a change in PEP (ΔPEP) and ΔCO. Each circle corresponds to one subject. In subjects with more expressed decrease in PEP (more negative ΔPEP), the higher increase in CO (higher ΔCO) was observed.

In the clinical or experimental settings where invasive measurement of basic cardiovascular measures is impractical non-invasive method of hemodynamic monitoring of the cardiovascular system on a beat-to-beat basis by ICG could be very useful (Peacock *et al.* 2000, Krzesiński *et al.* 2012, Parry *et al.* 2015). In previous studies, the validity of SV from ICG when assessing the changes in stroke volume was approved comparing its performance against invasive methods (thermodilution method, Fick method) during various conditions (Nieminen *et al.* 2000, Gujjar *et al.* 2008, McFetridge-Durdle *et al.* 2008, Burlingame *et al.* 2013, Kim *et al.* 2013). According to several validation studies, ICG was suggested as a reliable method to determine both the absolute value and changes of SV during different conditions (Yung *et al.* 2004, Brown *et al.* 2005, Schmidt *et al.* 2005). Although in some studies, the preciseness of ICG to estimate absolute values of stroke volume was challenged, its ability to

monitor trends in SV and measures derived from it was approved (Blohm *et al.* 2014, Fellahi *et al.* 2014, Kim *et al.* 2013, Gujjar *et al.* 2008). TFC is an ICG derived measure providing information on the fluid content in the thorax. It was demonstrated that TFC is a reliable parameter for evaluating the hemodialysis and diuretics induced changes in preload (Zalewski *et al.* 2013, Sanidas *et al.* 2009, Graziani *et al.* 2008, van De Water *et al.* 2005, Peacock *et al.* 2000). As a limitation of this measure, the changes in diaphragm position may also cause changes to electrical pathways of transthoracic sensing currents (Zhang *et al.* 2016) introducing a potential error to TFC as a measure of preload in our study during HUT. Taken together, our study was focused on the analysis of the changes in cardiovascular measures rather than their absolute values – therefore we assume that the distortion of results introduced by the non-invasiveness of the applied measurement approaches was not substantial.

Conclusions

We conclude that preejection period could be used as a sympathetic activity index in the conditions when the significant changes in preload, afterload or diastolic blood pressure do not occur. During various physiological and pathological states, the potential changes in other cardiovascular characteristics should be taken into consideration to properly interpret PEP changes.

Conflict of Interest

There is no conflict of interest.

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