



Relationships Between Systolic Time Intervals and Heart Rate During Initial Response to Orthostatic Manoeuvre in Men of Different Age

by

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An analysis of transient changes in physiological parameters in response to the standardized tests could be used to evaluate the efficiency of the regulatory processes. Relationships between systolic time intervals and heart rate following the action of standing up from the supine position were investigated in 41 healthy men, aged 20 to 59 years, classified into three groups: (22 to 26 yrs, n=14), (33 to 49, yrs, n=13) and (51 to 59 yrs, n=14). The protocol consisted of the following sequence: laying down (20 minutes) - standing up (8 minutes). Ejection time, pre-ejection period, electromechanical systole, heart rate and the length of R-R intervals were continuously calculated using automatized impedance cardiography and electrocardiogram. The ratio of ejection time to pre-ejection period in young men was significantly higher in comparison with the other groups. The ratio of ejection time to the length of R-R interval increased with age in supine position and after standing up when R-R interval was maximal. It was suggested that changes of ejection time to pre-ejection period during the orthostatic manoeuvre are rather the result of balance between heart rate and hemodynamic factors, than solely related to heart rate.

Key words: systolic function, orthostatic test, cardiovascular response, aging, transient response

Introduction

An analysis of transient changes in physiological parameters in response to the standardised tests could be used to evaluate the efficiency of the regulatory processes. The importance of the dynamic phase of the cardiovascular response to orthostatic manoeuvre was pointed out by several investigators (Johnson et al, 1965; Lipsitz, 1989; Janti, 1992) who discussed possible mechanisms of postural hypotension after standing up in elderly patients. Moreover, (Kassis, 1987) reported an abnormal cardiovascular response in heart rate (HR), total peripheral resistance (TPR), cardiac output (CO) and stroke volume (SV) to the orthostatic tilt test in patients with severe

congestive heart failure. Similarly, for blood pressure (BP) (based on follow-up research data), Davis et al. (1987), noticed a significantly higher mortality in diabetic hypertensive patients with the greatest (>20mmHg) drop in BP after standing up.

Aging causes the deterioration of muscle strength (Niewiadomski et al., 2007; Niewiadomski et al, 2008) and the decline of postural control system (Asaka and Wang, 2008). Also, aging can modulate the autonomic reflex responses, similarly as can systemic disease and pharmacological or toxic agents (Collins et al., 1980). Several investigators assessed the influence of aging on the dynamics of the initial HR response to postural changes. They showed the

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attenuation of the HR, or generally, cardiovascular response to standing/tilt with age (Ewing et al., 1978; Campbel et al., 1979; Wieling et al., 1982; Bergstrom et al., 1986; Piha, 1991; Cybulski, 1996; Cybulski and Niewiadomski, 2003). Systolic time interval (STI) analysis offers a quantitative, non-invasive and easy measure of left ventricular performance in man, because they are sensitive to changes in the inotropic state, pre-load and afterload (Lewis, 1983; Meijer et al., 2008). Also, STI measurement is well suited for studying the effect of pharmacological agents upon the heart (Boudoulas, 1990; Harjola et al., 2008). Some authors considered STI as very sensitive indices for detecting cardiac changes in moderate to advanced stages of hypertension (Hamada et al., 1990; McFetridge-Durdle et al., 2008). Others have shown that STI is affected by atherosclerosis, even when CO and left ventricular cavity dimension remain unchanged (Kazzam et al., 1991). STI have also been validated as a method to detect and monitor LV dysfunction in patients undergoing cardiac resynchronization therapy (Baker et al., 2004). It was noticed that STI (particularly pre-ejection period) may be used as a fast-response signal of upright position in rate-adaptive pacemakers (Ovaria et al., 1995). Some authors found that, in comparison to the control, contractility of the heart (measured by STI) is lower in patients with varicose veins (Singh & Sood, 2002). Also, it was observed that STI changes in hypertensive patients, in response to 60° head-up tilt, were attenuated (Viyayalakshimi et al., 2002).

Earlier, Weissler et al. (1961, 1968) reported that STI is strongly negatively related to heart rate (HR). The regression lines that they have proposed for pre-ejection period (PEP), ejection time (ET) and electro-mechanical systole (EMS) were used to compare cardiac timing for people with different resting HR. However, it was reported that in young men the STI versus HR regression lines have different regression coefficients in the supine position, from those in the standing position (60 seconds after standing up), during static effort or Valsalva manoeuvre (Mantysaari et al., 1984). The STI versus HR slopes might be also modified by physical training (Krzemiński et al., 1989).

It seems that new areas of possible STI applications are opened, as some authors, using receiver operating characteristics found PEP, ET and PEP/ET cutoff values in predicting high N-terminal pro-brain natriuretic peptide (Cheng et al., 2005). Also, there

were developed normal values of STI in children showing the effects of age, HR and body surface area (BSA) (Cui et al., 2008). Others suggested that ambulatory hemodynamic measurement of SV and STI provides a valid and reliable estimate of cardiac function in patients with hypertension, and may help further our understanding of pathophysiology of BP regulation (McFetridge-Durdle et al., 2008).

Although the importance of systolic time intervals (STI) in cardiology increases, their dynamics are less intensively recognised. Thus, we decided to analyze the transient period of STI in response to standing up, and their relations with age. In our previous research (Cybulski, 1996; Cybulski and Niewiadomski, 2003), we studied transient phase of the hemodynamic response to the orthostatic manoeuvre, using absolute values. We proposed the description of this phase (for STI, stroke volume and cardiac output), using several characteristic time points. This method allowed us to quantify the dampening effect of age on the hemodynamic response to standing up. However, there is a tendency to standardize electrical (e.g., QT) or mechanical intervals (PEP, ET or EMS), referring them to the length of the RR interval. This allows for comparison of the particular phases of cardiac cycle, regardless of the level of HR. In this paper we intend to use a "normalization approach", with the aim to check whether the pattern of STI response and the effect of age would remain after the elimination of the HR influence.

Material and methods

Subjects

Forty-one healthy men without any cardiovascular, respiratory or metabolic disorders participated in this study. The 12-lead ECG recordings taken from each subject did not show any abnormalities. The experimental protocol was carefully explained before starting the investigations and the informed consent was obtained from each subject. The experimental protocol was approved by the local ethical committee and all persons gave their informed consent prior to their inclusion in the study. The subjects did not report low orthostatic tolerance symptoms.

Table 1

<i>The characteristic of the subjects</i>					
	mean age \pm SD [years]	range of age [years]	mean body mass \pm SD [kg]	mean height \pm SD [cm]	number of subjects
group 1	24.1 \pm 1.1	22 -26	69.5 \pm 8.5	178.4 \pm 7.4	14
group 2	38.3 \pm 4.7	33 - 49	80.2 \pm 7.0	176.9 \pm 6.1	13
group 3	55.5 \pm 2.7	51 - 59	75.6 \pm 9.6	172.7 \pm 9.5	14

The subjects were classified into 3 groups according to the distribution of their age. The characteristic of the subjects is presented in Table 1.

Experimental procedure

The investigations were always carried out at the same time of day, under controlled conditions (23° to 26°C and 50-60% humidity). The measurements of HR and systolic time intervals were performed in the supine position, at least 20 min after lying down and then during 8 minutes of standing. The subjects changed their body position in 2 to 4 s on verbal command, without any help.

Ejection time (ET) and pre-ejection period (PEP) were calculated automatically, based on the impedance cardiography signals (ICG) (Cybulski et al., 1988).

Instrumentation and signal analysis

The ICG signals were detected using the RM 23 reometer (IBSPiE, Warsaw). The application of personal computer allowed continuous data collecting and automatic analysis of the ICG and ECG signals. The system was able to store and print results of ejection time (ET), pre-ejection period (PEP), R-R interval, and HR, as well as their mean values for each 5 s period. The detailed description of the program for automatic determination of STI and other hemodynamic parameters has been already published (Cybulski, 1988). The validity of STI measurements was checked earlier using pulse Doppler echocardiography method (Cybulski et al., 1993; Cybulski et al., 2004).

Data analysis

The initial R-R response to orthostatic manoeuvre was described by the following indices, according to Ewing et al. (1978), Campbel et al. (1979), Wieling et al. (1982), Bergstrom et al. (1986), and Cybulski (1996):

A [ms]= the mean length of R-R interval during the 60 s before changing the position (steady state),

B [ms] = the shortest R-R interval within the period 5-40 s after changing the position,

C [ms]= the longest R-R interval occurring during 40 s after B,

D [ms] = the length of the R-R interval 60 s after standing up,

E [ms] = the mean length of R-R interval at the end of 8 min of standing (steady state).

Also, ET, PEP and EMS values were analysed in the specified points (A, B, C, D, E) of R-R interval transient response to orthostatic manoeuvre.

Statistical analysis

The data presented as mean value \pm SD were analysed using the one way ANOVA. The Newman-Keuls' test was applied to evaluate the differences between the age groups. Also, the linear correlation method was applied to determine the relationships between HR and STI. The differences between the slopes of HR versus STI regression lines obtained in this paper, and those calculated according to the Weissler's formula (Weissler et al., 1961; Weissler et al., 1968), were analyzed using Student's t-test.

Results

The contribution of ET to R-R interval increased with age, which was manifested by significant differences at A, B and C points of the time course (Figure 1). It was also found that standing up causes the significant increase in the ET/RR ratio when the length of R-R was minimal (B). Moreover, the ET/RR ratio in the standing position was the same in both supine and standing steady states.

The contribution of PEP to R-R interval increased with age, which was manifested by significant differences in B and E points of the time course. It was found that standing up increased significantly the PEP/RR ratio when the length of R-R was minimal (B), as well as for the 60th second (D) and at the end of the standing period (E) (Figure 1.).

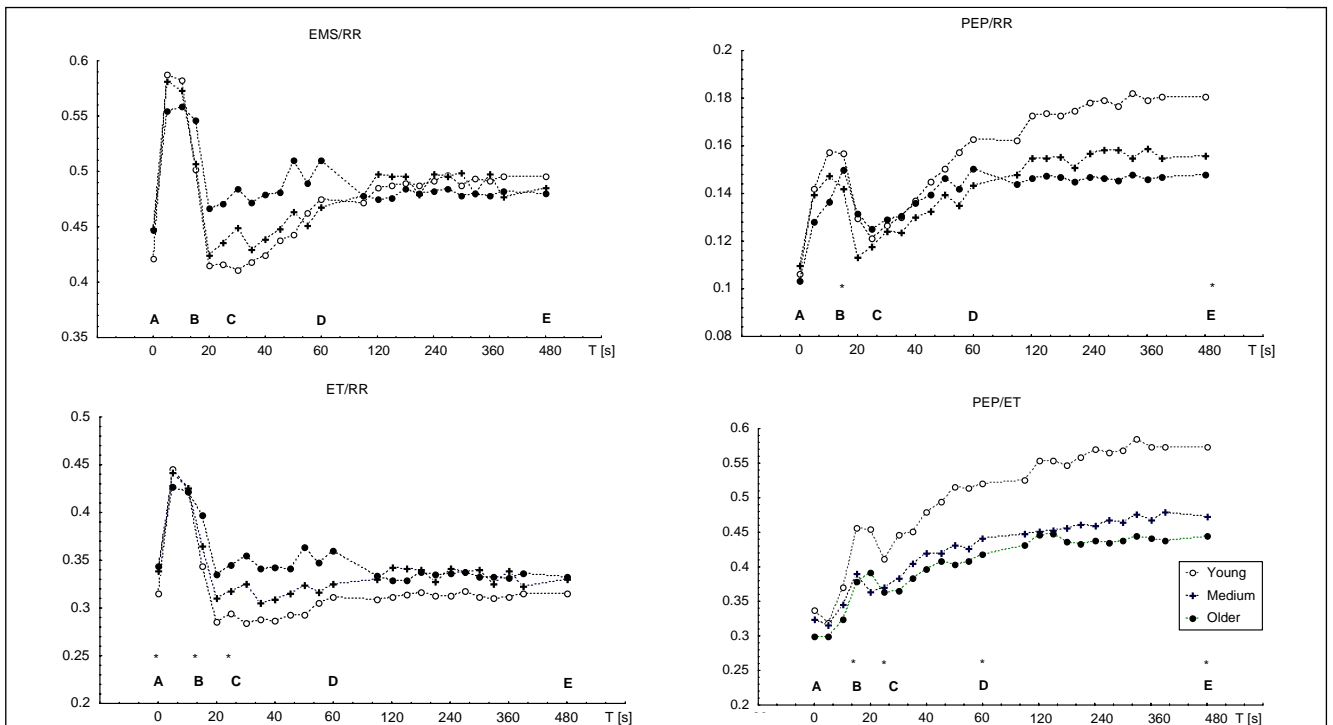


Fig. 1
 Changes in the ratios of ET/RR, PEP/RR, EMS/RR and PEP/ET during the orthostatic manoeuvre for 3 age groups (○ - means 22-26yrs, +: 33-49yrs, ● : 51-59yrs.) The differences between the groups were analysed in characteristic points of the test: A (supine), B (minimal value of R-R), C (maximal value of R-R), in the 60th second after standing up (D) and at the end of standing (E). Asterisk (*) - denotes statistical difference between the groups at the level of at least $p < 0.05$.

The contribution of EMS to RR interval did not differ with age, with exception of the values observed in B point when the ratio for the youngest group was significantly lower than for the middle-aged group. Standing up did not increase significantly the EMS/RR ratio (with an exception of that at B point).

The PEP/ET ratio significantly decreased with age and significantly increased during standing in all groups.

Table 2 summarizes data collected from all groups. The slopes of ET versus HR and EMS versus HR regression lines at different points of the orthostatic test were significantly different from the values postulated by, equal to -1.7 and -2.1, respectively. Moreover, the regressions between PEP and HR were insignificant, with an exception of the measurements in the supine position, where $b = -0.817 \pm 0.23$ significantly differed from the value of $b = -0.4$, as proposed by Weissler et al., (1968).

Discussion

STI measurement allows reliable, non-invasive evaluation of the left ventricular performance

(Lewis, 1983; Boudoulas, 1990; McFetridge-Durdle et al., 2008).

Pre-ejection period (PEP) is positively related to left ventricular pressure rise time, and negatively related to contractility. Prolongation of PEP is an index of heart failure (Weissler et al., 1961). Left ventricular ejection time (LVET or ET) is positively related to venous return, CO, SV, afterload and inversely related to myocardial inotropy (Weissler et al., 1961; Weissler et al., 1968). PEP/ET ratio, which is

Table 2

The slopes of the regression lines ETvsHR and EMSvsHR calculated in characteristic points of the orthostatic manoeuvre using data collected from all groups. A - denotes data collected in supine position, B and C - at maximal and minimal HR, respectively, D - data from 60th second after standing up, E - at 8th minute of standing

	ETvsHR		HR	EMSvsHR	
	b	s(b)		b	s(b)
A	-1.14**	0.27	64	-1.97	0.25
B	-1.02**	0.32	102	-1.41**	0.37
C	-	-	71	-0.99**	0.37
D	-0.86**	0.28	78	-	-
E	-1.82	0.36	81	-2.18	0.28
W	-1.7	-	-	-2.1	-

less sensitive to HR than other STI indices, negatively correlates with ejection fraction (EF) and contractility (Garrard, 1970; Zuber et al., 2008). It was also suggested, that acceleration of blood ejection during the first part of ET is related to PEP (Reitan et al., 1972).

STI were analysed in 5 points corresponding to HR changes: A-supine rest, B- minimum of R-R length, C- maximum of R-R length, D- 60s after standing and E- at the end of standing. Significant correlations of ET versus HR and EMS versus HR were found for most of the points in all groups of subjects. This finding remains in accordance with previous reports (Weissler et al., 1961; Weissler et al., 1968), where negative correlations between ET, EMS and HR were observed. However, in our study the slopes of the regression lines in the majority of cases were significantly lower than those calculated by Weissler et al. (1961, 1968). Moreover, contrary to their studies, our findings showed a lack of PEP versus HR correlations. Similar observations were described during the orthostatic test and Valsalva manoeuvre (Mantysaari et al., 1984). However, in our study, normalized RR data showed differences with age at points B and E.

The Weissler's indices were introduced as a simple tool for comparing the relationships between mechanical and electrical activity of the heart when its pacing rate is modified. However, these indices do not show an influence of changes in the afterload, atrial filling pressure and peripheral resistance on the timing relationships in the heart.

Calculation of the STI/RR ratios is another method of STI versus HR analysis, different from assumptive HR-corrected indices (De Mey et al., 1996). Results of the present paper showed that the orthostatic manoeuvre did not alter the ET/RR ratio in both supine and standing steady states. However, when R-R was minimal (B) and maximal (C), the ET/RR ratios became higher or lower, respectively. These alterations suggest that during postural transient hemodynamic changes, the mechanical adaptation of heart is not synchronized with pacing. Perhaps, during unsteady states, other pacing factors affect the STI (e.g., blood pressure alterations). It is worth noticing that the increase (absolute values) in ET versus HR slope from -1.14 (supine) to -1.817 (standing) coincided with the lack of differences between ET/RR ratios at the same time points. Moreover, ET/RR ratio increased with age in the supine position (A) and after standing up when R-R was

maximal (C). However, raw ET data correlated with age in all analysed points (Cybulski, 1996).

The correlations of PEP versus HR were not significant, however PEP/RR ratio increased during the standing up phase. There was also a tendency towards decreased PEP/RR ratio with age. This tendency was not observed for the raw PEP data (Cybulski, 1996). The increase of ET/RR with age, and the inverse tendency of PEP/RR, resulted in the lack of EMS/RR correlation with age.

Since the ET/RR and PEP/RR ratios were varying during the orthostatic test, we speculated on the response pattern of PEP/ET. The orthostatic manoeuvre caused a significant increase in the PEP/ET ratio (in young subjects from 0.34 to 0.58), which confirmed the data collected during the passive tilt (Stafford et al., 1970). Further, the PEP/ET ratio in young men was significantly higher in comparison with the other groups, which may result from better heart contractility in younger subjects. Generally, the increase of PEP/ET ratio during the transient phase of the orthostatic manoeuvre is caused by the increase in PEP/RR ratio. Moreover, PEP/ET ratio, which correlates with ejection fraction, significantly decreased with age (Lewis, 1983).

We still do not know why the STI versus HR relationships change with age. It could be the effect of mechanical stiffening of the cardiovascular system with age, changes in baroreceptor characteristics, or the modified balance between sympathetic and parasympathetic systems (Meijer et al., 2008). Some authors noticed (however examining only young patients with unexplained syncope) that postural changes of STI were independent of vagal tone (Ovadia et al., 1995). This may suggest that the STI versus HR relationship is not affected by the autonomic system, or this influence occurs in older subjects.

Conclusions

We found that the influence of HR on the transient phase of STI during the orthostatic manoeuvre, however dominating, is not the only factor. It seems that the changes in ET and PEP during the orthostatic manoeuvre are rather the result of a balance between HR and other factors (possibly SV, BP, peripheral resistance and venous return), than solely related to HR. The effect of other factors is more pronounced in the transient period (analyzed points B, C, D). This is possibly due to the modification of

those factors with age influence on the STI versus HR relationships.

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