

Presyncopal Cardiac Contractility and Autonomic Activity in Young Healthy Males

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Summary

We investigated non-invasively cardiac contractility and autonomic nervous activity during presyncopal orthostatic stress induced in healthy humans. A graded orthostatic stress (GOS) paradigm, consisting of head-up tilt (HUT) combined with lower body negative pressure (LBNP) of increasing magnitude, was used to reach a presyncopal end-point in 15 healthy adults. Continuous beat-to-beat hemodynamic and autonomic parameters were recorded. From supine control (C1) to presyncope (PS), total peripheral resistance index (TPRI) decreased from 2300 ± 500 to 1910 ± 320 $\text{dyne} \cdot \text{s} \cdot \text{m}^2 / \text{cm}^5$ ($p=0.004$), index of contractility (IC) from 59 ± 14 to 27 ± 6 $1000/\text{s}$ ($p<0.0001$), left ventricular working index (LVWI) from 5.2 ± 1.3 vs. 3.6 ± 0.6 $\text{mmHg} \cdot \text{L} / (\text{min} \cdot \text{m}^2)$ ($p=0.0001$) and acceleration index (ACI) from 65 ± 18 vs. 54 ± 15 $100/\text{s}^2$ ($p=0.04$). Low frequency variation of diastolic blood pressure ($\text{LF}_{\text{nu}}\text{dBP}$) increased from 51 ± 14 to 67 ± 11 % ($p=0.0006$) and of systolic blood pressure ($\text{LF}_{\text{nu}}\text{sBP}$) from 50 ± 6 vs. 67 ± 8 % ($p<0.0001$). High frequency variation of RR-interval ($\text{HF}_{\text{ms}}\text{RRI}$) decreased from 385 ± 320 to 38 ± 43 ms^2 ($p=0.001$). From late GOS (G3) to PS, TPRI decreased from 2540 ± 640 to 1910 ± 320 $\text{dyne} \cdot \text{s} \cdot \text{m}^2 / \text{cm}^5$ ($p=0.003$), IC from 35 ± 6 to 27 ± 6 $1000/\text{s}$ ($p=0.003$), LVWI from 4.6 ± 0.9 to 3.6 ± 0.6 $\text{mmHg} \cdot \text{L} / (\text{min} / \text{m}^2)$ ($p=0.003$), $\text{LF}_{\text{nu}}\text{sBP}$ from 71 ± 8 to 67 ± 8 % ($p=0.03$), $\text{LF}_{\text{mmHg}}\text{dBP}$ from 6.6 ± 4.0 to 4.8 ± 2.9 mmHg^2 ($p=0.0001$), $\text{LF}_{\text{mmHg}}\text{sBP}$ from 9.7 ± 7.8 to 7.4 ± 4.8 mmHg^2 ($p=0.01$). $\text{HF}_{\text{nu}}\text{RRI}$ increased from 19 ± 8 to 28 ± 13 % ($p=0.008$). Myocardial contractility indices and parameters of sympathetic activity were reduced in the presyncopal state, while parasympathetic activity was increased. This suggests a decrease in cardiac contractility during orthostatically induced presyncope in healthy subjects.

Key words

Hemodynamics • Total peripheral resistance • Blood pressure • Impedance cardiography • Sympathetic withdrawal • LBNP • HUT

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Introduction

Presyncope is a state immediately preceding a syncopal event, defined as a sudden, brief, transient loss of consciousness, with a loss of postural tone (Kapoor 2000). ‘Physiological’ syncope within the frame of an orthostatic stress paradigm develops as a result of critically diminished cardiac preload due to low venous return. Once brain perfusion is reduced below a critical level, a “neurocardiogenic” reflex (“vasovagal attack”) is triggered that causes vasodilation, reduces heart rate, cardiac output, and consequently blood pressure, and loss of consciousness is imminent. Although the trigger for the rapid and sudden switch in autonomic responses still remains elusive and poorly understood, it has frequently been emphasized that the autonomic nervous system plays a key role as a final common pathway leading to syncope (Morillo *et al.* 1994, Furlan *et al.* 1998, Mangin *et al.* 2001).

It is unclear how exactly sympathetic activity changes in a presyncopal situation: power spectral analysis of RR variability indicates increased, unchanged,

or reduced sympathetic activity immediately preceding a vasovagal event, and microneurography has revealed rather unpredictable patterns (Mosqueda-Garcia *et al.* 1997). Pagani *et al.* (1997) have concluded that sympathetic activation is associated with an increase of the LF component of both muscle nerve sympathetic activity (MSNA) and systolic arterial pressure (SAP). They suggested to use the changes in LF of SAP variability as a marker of changes in sympathetic efferent activity. They also found that the HF component of MSNA variability in normalized units was closely related with the HF component (in normalized units) of RRI (Pagani *et al.* 1997).

Vaso-vagal syncope might be triggered by a stimulation of cardiac receptors, and inadequate stimulation of mechanoreceptors may be caused by excessive myocardial contractility (Oberge and Thoren 1972). While some found powerful presyncopal myocardial activity (Shalev *et al.* 1991), others observed no difference (Bellard *et al.* 2003) or even decreased myocardial contractility (Liu *et al.* 2000). Peak endocardial acceleration (PEA) measurements provided the indication for decreased myocardial contractility during fainting (Mangin *et al.* 2001) as did impedance cardiography (Mitro and Hijová 2006). However, these studies were carried out in patients.

Based on the hypothesis of clear indication of decreasing presyncopal myocardial contractility together with a shift away from sympathetic towards parasympathetic activity, the aim of this study was to investigate non-invasively indices of cardiac contractility, autonomic nervous activity, and hemodynamics during and after presyncopal orthostatic stress in healthy humans.

Materials and Methods

Subjects

To avoid effects of confounding variables such as height, gender or athletic training on orthostatic tolerance (Goswami *et al.* 2008) we selected fifteen healthy males (31 ± 2 years, 75 ± 3 kg, 182 ± 2 cm, BMI 23 ± 1 kg/m²) with no history of syncope, pathological condition (neurological, cardiovascular, endocrine) and not on any medication. Test subjects abstained from alcohol, smoking and caffeine as well as from vigorous exercise for 48 h prior to examination, and were advised not to change their fluid and salt intake as governed by their usual dietary habits. A light breakfast with sufficient

fluid intake was allowed before the test. All studies occurred between 09:00 and 12:00 h in an air-conditioned, semi-dark room (temperature 22 ± 1 °C, humidity 55 %). The Graz Medical University's Ethics Committee approved the study, and written informed consent was obtained from each subject.

Experimental protocol

We used the Adaptive and Spaceflight Physiology Institute's multi-stimulation test device (www.meduni-graz.at/iap/AHST.htm) that allows for < 10 s postural changes and LBNP build-up (Fig. 1, below). The sealing was maintained at the iliac crest, as sealing position has been shown to affect hemodynamic responses (Goswami *et al.* 2009). Test subjects were secured and had access to an emergency shutdown (automatic return to supine and pressure neutralization) at all times. The experiment commenced with 5 min 70° passive head-up tilt (HUT). It was followed by graded LBNP, which started with 20 mmHg suction, and was increased by 10 mmHg each in 3-min intervals, until presyncope occurred. The criteria of presyncope were a) blood pressure drop below systolic 80 mmHg or by ≥ 25 mmHg/min, diastolic by ≥ 15 mmHg/min, and/or heart rate decrease by ≥ 15 bpm, and b) lightheadedness, dizziness, visual disturbances, nausea, stomach awareness, clammy skin, excessive sweating, or skin pallor (Hinghofer-Szalkay *et al.* 2006).

Hemodynamics

Blood pressure was monitored using the Penaz principle (Wesseling 1996). Total peripheral resistance index (TPRI) was calculated as mean arterial blood pressure/cardiac index and mean arterial blood pressure as calculated from diastolic and systolic pressures, respectively: $MAP = dBP + 1/3 (sBP - dBP)$. Cardiac index (CI), which relates heart performance to the size of the individual, was calculated as cardiac output/body surface area. Stroke index was calculated as stroke volume/body surface area. Impedance cardiography, in which the changes in thoracic impedance are converted to reflect changes in thoracic fluid/volume over time, was performed based on the original Kubicek approach but using an improved estimate of thoracic volume (Task Force Monitor, TFM®).

ECG/impedance electrodes were positioned together with upper arm and finger blood pressure cuffs (Fortin *et al.* 2006). Electrode strips were placed at the neck and thoracic regions, the latter specifically at the

midclavicular line at the xiphoid process level. The method has been described in detail elsewhere (Fortin *et al.* 2006). Recorded and calculated data were stored real-time beat-to-beat throughout the entire experiment.

Heart rate and blood pressure variability

Low (LF: 0.05-0.17 Hz) and high frequency (HF: 0.17-0.40 Hz) power components of RR-intervals (RR), diastolic blood pressure (dBp) and systolic blood pressure (sBP) were evaluated and given in absolute values (ms^2) and normalized units (nu) applying an autoregressive method, as normalization minimizes disruptive effects of changes in total power (Camm *et al.* 1996). The referring frequency bands indicate autonomic modulation of the sinoatrial node and of vasomotion (Camm *et al.* 1996). In the present study we used changes in the LF range of arterial blood pressure to assess information about sympathetic activity, as it is generally considered to be associated with sympathetic nerve activity (Malliani *et al.* 1991, Pagani *et al.* 1997). We used changes in the HF range of heart rate variability (HF_RRI) to assess parasympathetic activity because HF_RRI is primarily mediated by parasympathetic nerve modulation, whereas LF_RRI is probably affected by both parasympathetic and sympathetic modulations (Pagani *et al.* 1997, Stauss 2003).

Myocardial contractility parameters

Myocardial contractility parameters were derived through impedance cardiography measurement. The index of contractility (IC) reflects the aortic peak flow and it is the maximum impedance changes ($\Delta Z/\Delta t_{\text{max}}$) normalized to the ground impedance Z_0 . The acceleration index (ACI) refers to the maximum aortic

blood acceleration as a function of time and is defined as $\Delta^2 Z/\Delta t_{\text{max}}^2$. The left ventricular work index (LVWI) was calculated as (mean blood pressure – pulmonary capillary occlusion pressure (fixed to 7 mmHg)) * cardiac index * const.

Data acquisition and analysis

Data from distinct protocol time points were used to obtain the defined parameter patterns, particularly from the period preceding and immediately after presyncope. In each test, the following protocol points were identified: Supine control (C1), early tilt (G1), late tilt (G2), late graded orthostatic stress [GOS] (G3), presyncope (PS), early recovery (PG1) and late control (PG2). All data are means from observation periods: C1, 60 s before GOS; G1, the immediate 60 s after commencing HUT; G2, the last 60 s of HUT; G3, the last minute of LBNP 20 (this was the only LBNP step finished by all test subjects); PS, the last minute of GOS preceding presyncope; PG1, the first sixty seconds after GOS; and PG2, the last 60 s before termination of the experiment, which was 15 min after return to supine.

Statistical analysis

Variables were tested for normality using the D'Agostino & Pearson omnibus normality test and expressed as mean value \pm S.D. Repeated measures ANOVA with Dunnett *post-hoc* or the Friedman test with Dunn *post-hoc* testing were used to test for changes in all tested variables and parameters with orthostatic loading (C1 compared to all other time periods). All reported p values are two-sided. For all tests, significance was set at $p \leq 0.05$. All analyses were performed using GraphPad Prism 5 software.

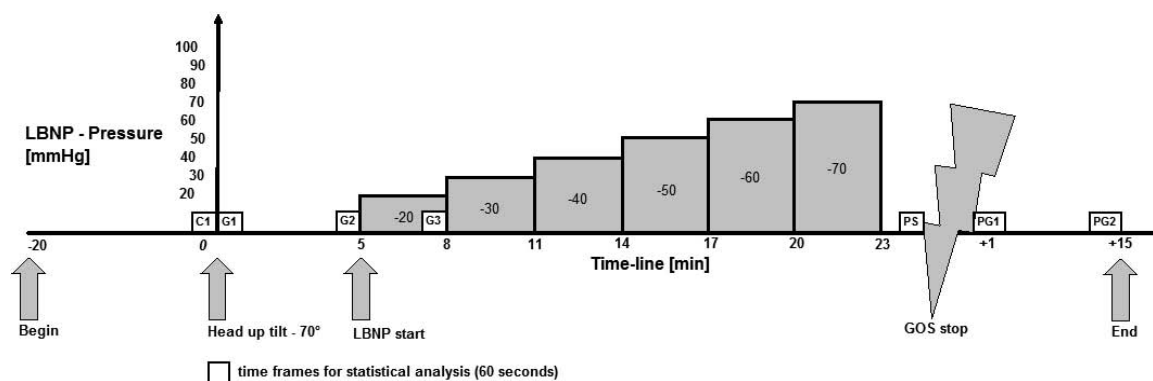


Fig. 1. Experimental protocol and details of specific points at which the data were analyzed. C1: supine control; G1: early tilt; G2: late tilt; G3: late GOS; PS: presyncope; PG1: early recovery; PG2: late control.

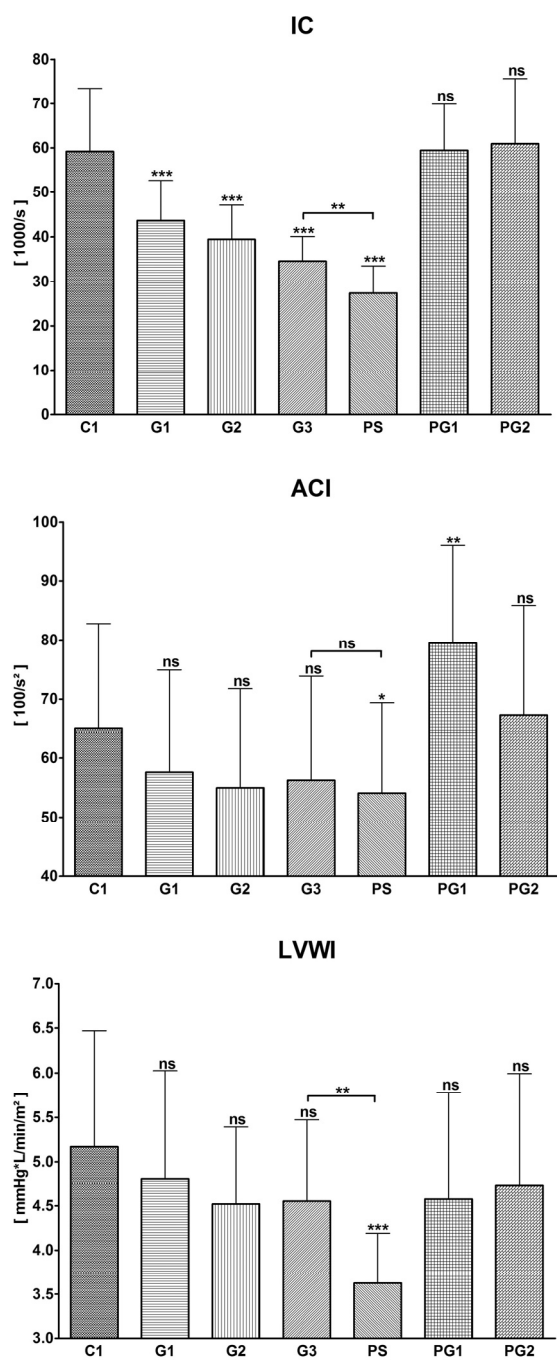


Fig. 2. Changes in myocardial contractility parameters during and after GOS. IC: index of contractility, ACI: acceleration index, LVWI: left ventricular working index. C1: supine control; G1: early tilt; G2: late tilt; G3: late GOS; PS: presyncope; PG1: early recovery; PG2: late control. Bars show means \pm S.D. ***, $P < 0.0005$; **, $P < 0.005$; *, $P < 0.05$.

Results

Mean orthostatic tolerance time was 13 ± 1 min. Six test subjects showed a pure vasodepressor reaction prior to presyncope, five a mixed (cardioinhibitory and vasodepressor) reaction and four showed symptoms like

lightheadedness, sweating, nausea, and visual disturbances.

Hemodynamic changes during and after GOS

Compared to supine control (C1) SI, CI, TPRI and blood pressure values were reduced and HR and TI increased in presyncope (PS) (Table 1). After GOS, HR, SI, and CI quickly returned to normal (not different from C1), while mean arterial blood pressure and TPRI was below C1 levels at PG1, and TI remained elevated at PG1 and PG2 (Table 1). In comparing late GOS (G3) with PS, diminished TPRI was observed (Table 1).

Changes in myocardial contractility parameters during and after GOS

Fig. 2 shows the myocardial contractility indices IC, ACI, LVWI at defined protocol times. IC decreased stepwise during GOS (59 ± 14 to 27 ± 6 1000/s; $p < 0.0001$). ACI was significantly decreased (65 ± 18 to 54 ± 15 100/s²; $p = 0.04$) only at PS, and increased above C1 at PG1 (65 ± 18 to 80 ± 17 100/s²; $p = 0.002$). Similarly, LVWI was reduced at PS (5.2 ± 1.3 to 3.6 ± 0.6 mmHg·L/min/m²; $p < 0.0001$) (Fig. 1). In late GOS (G3), as compared with PS, IC (35 ± 6 to 27 ± 6 1000/s; $p = 0.003$) and LVWI (4.6 ± 0.9 to 3.6 ± 0.6 mmHg·L/(min·m²); $p = 0.003$) were decreased, whereas ACI was unchanged (Fig. 2).

Autonomic changes during and after GOS

LF_{nu}dBp and LF_{nu}sBP increased in a stepwise fashion with a peak at G3 (51 ± 4 to 70 ± 15 %; $p < 0.0001$ and 50 ± 6 to 71 ± 8 %; $p < 0.0001$, respectively) and returned to supine rest values after GOS (Fig. 3). Even at presyncope (PS), both LF_{nu}dBp (51 ± 14 to 67 ± 11 %; $p = 0.0006$) and LF_{nu}sBP (50 ± 6 to 67 ± 8 %; $p < 0.0001$) increased compared to supine control. Compared late GOS (G3) with presyncope (PS) LF_{nu}sBP fell from 71 ± 8 to 67 ± 8 % ($p = 0.03$). There was a presyncope decrease during G3, in particular LF_{mmHg}dBp fell from 6.6 ± 4.0 to 4.8 ± 2.9 mmHg² ($p = 0.0001$) and LF_{mmHg}sBP from 9.7 ± 7.8 to 7.4 ± 4.8 mmHg² ($p = 0.01$) (Fig. 3).

HF_{nu}RRI decreased significantly at G2 (35 ± 15 to 17 ± 7 %; $p = 0.0002$) and G3 (35 ± 15 to 18 ± 8 %; $p = 0.003$) compared to supine control (C1) and increased from G3 (19 ± 8 to 28 ± 13 %; $p = 0.01$) to presyncope (PS) (Fig. 4). During GOS HF_{ms}RRI decreased in a stepwise fashion (385 ± 320 to 38 ± 43 ms²; $p = 0.0009$) and returned quickly, after cessation of GOS, to C1 levels (Fig. 3). In comparing late GOS (G3) with presyncope (PS), diminished values of HF_{ms}RRI were observed (103 ± 77 to 39 ± 43 ms²; $p = 0.003$) (Fig. 4).

Table 1. Hemodynamic changes during and after GOS (graded orthostatic stress).

	HR [bpm]	SI [ml/m ²]	CI [l/(min* m ²)]	TI [Ω]	sBP [mmHg]	dBP [mmHg]	MAP [mmHg]	TPRI [dyne*s*m ² / cm ⁵]
C1	75±15	50±10	3.7±0.7	34.7±3.8	137±17	90±16	106±16	2306±496
G1	91±18**	37±5***	3.4±0.5	36.3±4.1***	136±21	95±22	109±20	2573±586
G2	93±14**	34±4***	3.2±0.4***	36.7±4.2***	135±17	95±12	109±12	2691±448*
G3	106±18***	31±4***	3.3±0.4*	37.8±4.4***	129±20	95±22	106±20	2543±642
PS	128±26***	26±4***	3.2±0.3**	38.9±4.6***	101±18***	75±14*	83±14***	1913±321*
PG1	87±20	46±8	3.8±0.7	36.2±4.2***	121±21	76±15	91±14*	1966±289*
PG2	65±10	53±10	3.4±0.7	35.4±4.2*	123±38	79±26	94±30	2375±554

Heart rate (HR), stroke index (SI), cardiac index (CI), thoracic impedance (TI), systolic blood pressure (sBP), diastolic blood pressure (dBP), mean arterial blood pressure (MAP), total peripheral resistance index (TPRI). Values are mean ± S.D. C1: supine control; G1: early tilt; G2: late tilt; G3: late GOS; PS: presyncope; PG1: early recovery; PG2: late control.***, P<0.0005; **, P<0.005; *, P<0.05.

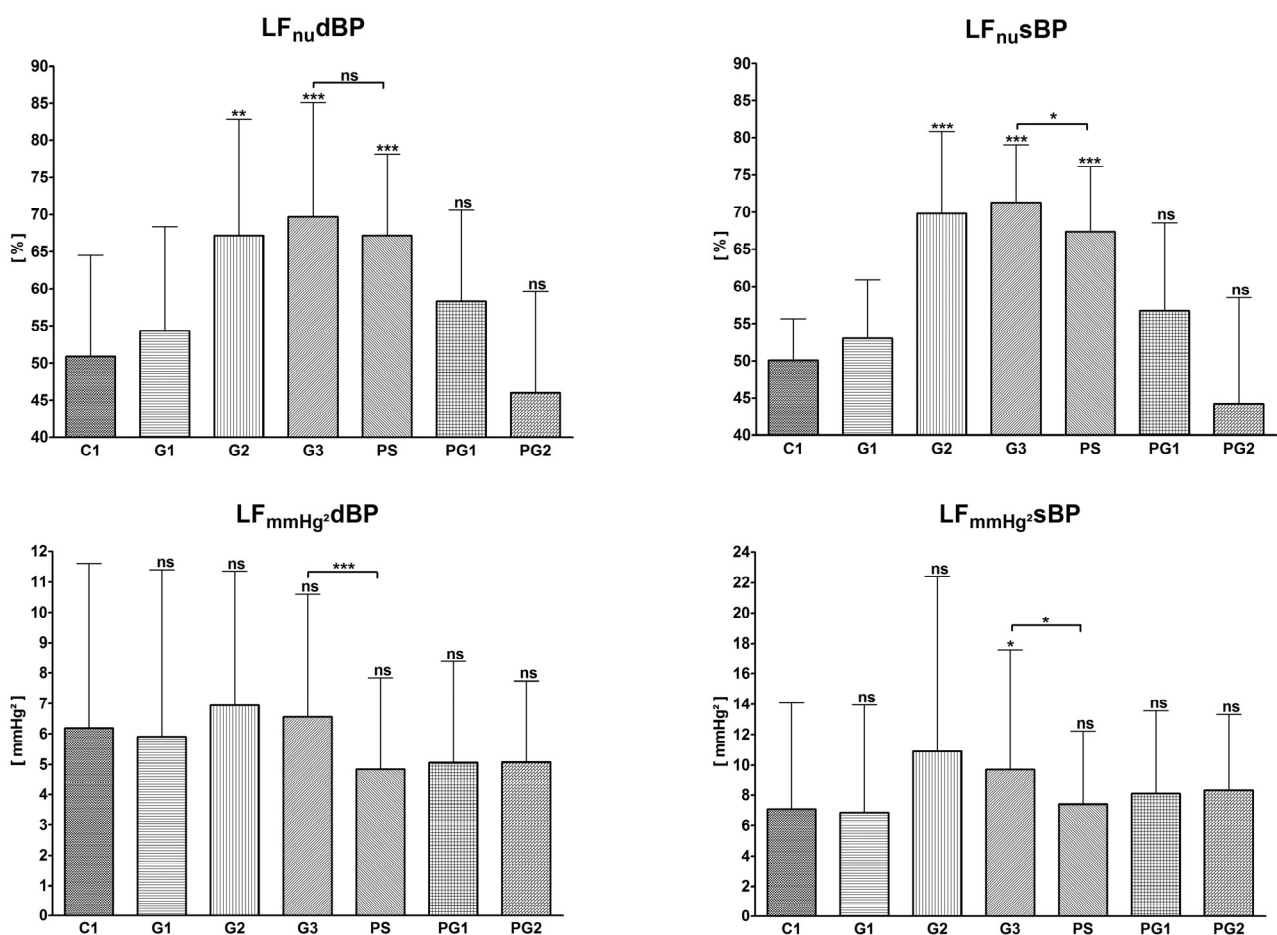


Fig. 3. Autonomic changes during and after GOS. $LF_{nu}dBP$: low frequency of diastolic blood pressure, normalized values. $LF_{nu}sBP$: low frequency of systolic blood pressure, normalized values. $LF_{mmHg^2}dBP$: low frequency of diastolic blood pressure, absolute values. $LF_{mmHg^2}sBP$: low frequency of systolic blood pressure, absolute values. Bars show means ± S.D. ***, P<0.0005; **, P<0.005; *, P<0.05.

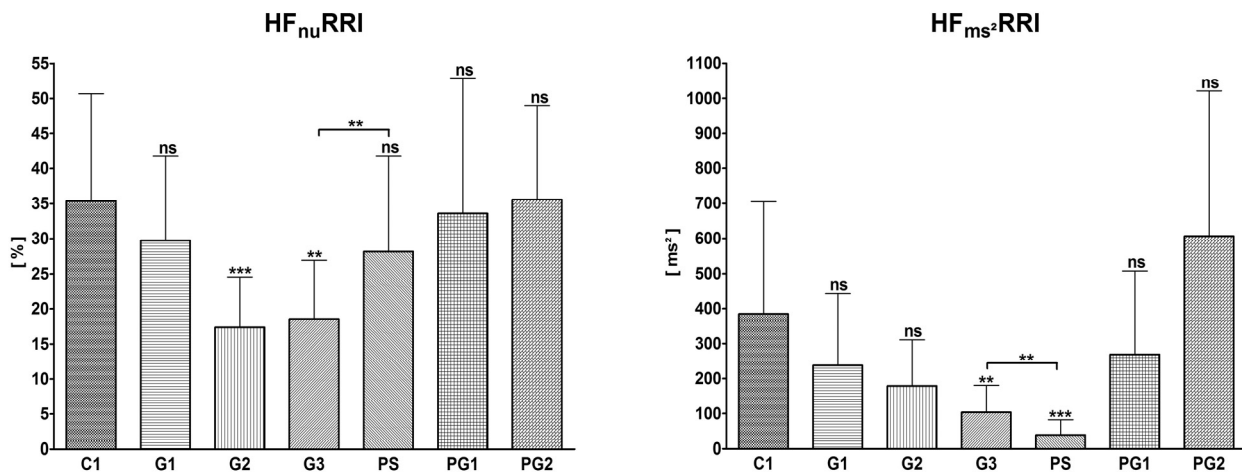


Fig. 4. Autonomic changes during and after GOS. HF_{nu}RRI: high frequency variation of RR-interval, normalized values. HF_{ms²}RRI: high frequency variation of RR-interval, absolute values. C1: supine control; G1: early tilt; G2: late tilt; G3: late GOS; PS: presyncope; PG1: early recovery; PG2: late control. Bars show means \pm S.D. ***, $P < 0.0005$; **, $P < 0.005$; *, $P < 0.05$.

Discussion

We present the evidence of reduced myocardial contractility, decreased total peripheral resistance and diminished sympathetic activity in healthy men undergoing orthostatically induced presyncope.

Several clinical studies have investigated myocardial contractility and changes in autonomic variables. Mizumaki *et al.* (1995) used echocardiography to assess the contractility status and power spectral analysis for HRV measurements. Mangin *et al.* (2003) employed peak endocardial acceleration (PEA) as an index of myocardial contractility and measured HRV through power spectral analysis. However, some investigators did not incorporate autonomic variables in their myocardial contractility studies but used impedance cardiography to assess myocardial contractility (Mitro and Híjová 2006). In the present investigation, we focused on changes in hemodynamic and myocardial contractility combined with autonomic activity using graded orthostatic stress (GOS) to provoke presyncope in non-medicated healthy male test subjects. We have previously used the combined head up tilt and graded lower body suction to study hemodynamic and neurohormonal responses to extreme orthostatic stress (Grasser *et al.* 2009), effect of Chinese herbs on cardiovascular responses (Gao *et al.* 2008) and more recently, to demonstrate post-reactive hyperemia in the human liver (Hinghofer-Szalkay *et al.* 2008).

Hemodynamic changes

With increasing orthostatic stress there was a

steady increase in thoracic impedance from supine control to presyncope, suggesting increasing central hypovolemia (Pomerantz *et al.* 1970, Cai *et al.* 2000). Neurally mediated syncope is usually triggered by peripheral blood pooling, low venous return, and a “partially emptied” heart (Zaqqa and Massumi 2000); increased parasympathetic activity finally reduces heart rate, rendering cardiac output insufficient to support proper brain perfusion (Lurie and Benditt 1996). Brown and Hainsworth (2000) observed total peripheral resistance to fall from a level elevated 40 % above supine values two minutes before, to 20 % one minute before presyncope, indicating build-up of peripheral loss of vascular tone. We found total peripheral resistance index already decreased below supine control values one minute before presyncopal signs occurred.

Differences are conceivably dependent on the protocol used. Brown *et al.* (2000) used 20 mmHg steps every 10 min; we increased LBNP intensity by 3-min steps. We used impedance cardiography to calculate total peripheral resistance index from the baseline, while Brown *et al.* (2000) used brachial artery ultrasonography to indirectly assess cardiac output. We found a marked drop in resistance index from the last minute of tolerated LBNP to presyncope, indicating sympathetic withdrawal shortly before presyncope. It is possible that the elevated circulating norepinephrine (NE) and epinephrine (E) contributed to a beta-adrenergic receptor (β AR) downregulation in humans (Bristow *et al.* 1982). When receptors in intact cells or tissues are exposed to agonists, there is often a rapid decline in responsiveness. This process is called receptor desensitization (Pippig *et al.*

1993). The time frames over which these processes occur range from seconds (phosphorylation) to minutes (endocytosis) and hours (down-regulation). In terms of β_2 -AR the extent of receptor desensitization leads to attenuation of agonist potency and maximal responsiveness (Pippig *et al.* 1993, Fergusson 2001). The same might hold for α_1 -AR subtypes, which are the prime mediator of smooth muscle contraction (Piascik and Perez 2001). Experiments with knockout mice suggest that α_{1A} -AR is the dominant adrenoceptor for vascular smooth muscle contraction (Piascik and Perez 2001). Rudner *et al.* (1999) hypothesized that α_{1A} -AR mediated contraction may account for generalized splanchnic vasoconstriction during stress in humans. It is conceivable that elevated NE and E levels (both were observed to be elevated at presyncope compared to baseline, data not shown) led to a desensitization of adrenergic receptors, which would explain our observation of decreased myocardial contractility indices and peripheral resistance preceding syncope.

Another possible explanation could be metabolically driven vasodilation, which was found after strenuous exercise (Clifford and Hellsten 2004). Convertino and Sather (2000) have proposed that under orthostatic stress, beta adrenergic-induced tachycardia is a primary mechanism for the maintenance of arterial blood pressure. Our observed drop of total peripheral index decreased the mean arterial pressure in the last 60 s before presyncope. This is in agreement to previous findings (El-Bedawi and Hainworth 1994, Julu *et al.* 2003, Leloir *et al.* 2003) that arterial pressure was no longer stabilized in this situation.

After the combined head-up tilt and LBNP, the heart rate, stroke index and cardiac index returned to supine control values within one minute, whereas blood pressure was still reduced. This could be attributed to the still below supine control levels of peripheral resistance at this point. Thoracic impedance stayed elevated above baseline for 15 min (PG2), probably due to fluid loss during GOS (Evans *et al.* 2004). However, cardiac output was not different from supine control.

Myocardial contractility indicators changes

Sudden reductions in venous return as caused by orthostatic stress primarily involve chronotropic instead of inotropic compensation (Guazzi *et al.* 1995). Indeed, all contractility indices decreased with presyncope in our study; index of contractility decreased progressively with increasing orthostatic load. Similarly,

acceleration index and left ventricular working index were also decreased significantly at presyncope. Overall, the observations on cardiac contractility with (pre)syncope are controversial. Shalev *et al.* (1991) found powerful myocardial activity using echocardiography, but others observed no difference in myocardial contractility (Bellard *et al.* 2003) or even decreased contractility (Liu *et al.* 2000), also by using echocardiography. Using impedance cardiography, Mitro and Hijová (2006) also provided evidence against increased contractility. Mangin *et al.* (2001), using peak endocardial acceleration as index of myocardial contractility, found that cardiac inotropy increased gradually during the entire testing in a head-up tilt positive subgroup, but they also observed a decrease in myocardial contractility during fainting.

Following 60 s of stress cessation, the index of contractility and left ventricular working index were not different from baseline levels. However, acceleration index, was increased 60 s following the termination of graded orthostatic stress. A recent study, which also used impedance cardiography, observed a trend towards increased myocardial contractility one minute after syncope (Mitro *et al.* 2006). These authors speculated that the increased inotropy might represent a compensatory mechanism originating from a sympathetic reflex response to increased peripheral blood pooling.

Heart rate and blood pressure variability

Vasovagal syncope is associated with a sudden onset of hypotension, often in combination with bradycardia or transient asystole, probably due to sympathetic withdrawal. Shortly before presyncope, we observed low frequency power components of diastolic and systolic blood pressure increased, whereas absolute values showed no change compared to baseline. As total power variance is reduced, the absolute power of low frequency appears to be unchanged compared to the rest (Camm *et al.* 1996). Low frequency power components of diastolic and systolic blood pressure both decreased between late graded stress and presyncope, indicating sudden sympathetic withdrawal which is in agreement with previous findings and matches the decrease in vascular resistance index, acceleration index and left ventricular working index. The high frequency power component of RR-interval ($HF_{ms}RRI$) was below baseline levels at presyncope, while $HF_{nu}RRI$ remained unchanged. Using power spectral analysis of heart rate variability, Mizumaki *et al.* (1995) also found decreased presyncopal high frequency power component of RR-

interval in their control group of healthy men. Similarly, Mangin *et al.* (2001) found a marked presyncopal drop in the high frequency power component of RR-interval in subjects prone to syncope. However, they used isoproterenol infusion to provoke syncope in their test subjects and this could influence the autonomic system. We observed HF_{nu}RRI decreased at end of tilt phase and at late graded orthostatic stress compared to controls, which suggests low parasympathetic activity. From late graded stress to presyncope, however, HF_{nu}RRI increased, indicating vagal activation shortly before presyncopal signs or symptoms occurred. This is in agreement with previous observations (Furlan *et al.* 1998, Kamiya *et al.* 2005). Piccirillo *et al.* (2004) found diminished HF_{nu}RRI in the early stage of head-up tilt but no change from their first recording to their second, denoted as the last 256 beats before syncope. This discrepancy to our observation could be attributed to the breathing patterns, as our subjects were allowed to breathe freely. Higher breathing frequency in the presyncopal state elevates the HF_{nu}RRI (Piccirillo *et al.* 2004).

Limitations

We studied healthy males with no history of syncope. We cannot generalize our findings to patients with vasovagal syncope or orthostatic intolerance. To simulate real life scenario characterized by spontaneous

ventilatory activity, we did not control breathing, as this is known to influence heart rate and blood pressure variability (Piccirillo *et al.* 2004).

Conclusions

Myocardial contractility indices and parameters of sympathetic activity were reduced in the presyncopal state, while indication of parasympathetic activity was increased. This suggests a decrease in cardiac contractility during orthostatically induced presyncope in healthy young subjects. Additional investigations are warranted to confirm these findings across a larger age range, in both men and women and in non-healthy subjects.

Conflict of Interest

There is no conflict of interest.

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