The cardiovascular response to lower body negative pressure in humans depends on seal location

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Running Head: Location of LBNP sealing

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Abstract

We tested whether seal location at iliac crest (IC) or upper abdomen (UA), before and during lower body negative pressure (LBNP), would affect thoracic electric impedance, hepatic blood flow, and central cardiovascular responses to LBNP. After 30 min of supine rest, LBNP at -40 mmHg was applied for 15 min, either at IC or UA, in 14 healthy males. Plasma density and indocyanine concentrations assessed plasma volume changes and hepatic perfusion. With both sealings, LBNP-induced effects remained unchanged for mean arterial pressure (-3.0 ± 1.1 mmHg), cardiac output (-1.0 L min^{-1}), and plasma volume (-11%). Heart rate was greater during UA (80.6 ± 3.3 bpm) than IC (76.0 ± 2.5 bpm) ($p < 0.01$) and thoracic impedance increased more using UA (3.2 ± 0.2 Ω) than IC (1.8 ± 0.2 Ω) ($p < 0.0001$). Furthermore, during supine rest, UA was accompanied by lower thoracic impedance (26.9 ± 1.1 vs 29.0 ± 0.8 Ω, $p < 0.001$) and hepatic perfusion (1.6 vs 1.8 L min^{-1}, $p < 0.05$) compared to IC. The data suggest that the reduction in central blood volume in response to LBNP depends on location of the applied seal. The sealing in itself altered blood volume distribution and hepatic perfusion in supine resting humans. Finally, application of LBNP with the seal at the upper abdomen induced a markedly larger reduction in central blood volume and, in turn, splanchnic blood flow and heart rate increase than when the seal was located at the iliac crest.

Key words: abdominal compression, central blood volume, orthostasis, splanchnic blood flow, thoracic electrical impedance.

Introduction

In humans hypovolemic and orthostatic stress can be simulated by application of lower body negative pressure (LBNP), as this method leads to peripheral blood pooling and consequently, central hypovolemia (Gao *et al.* 2008, Grasser *et al.* 2008, Hinghoer-Szalkay *et al.* 2008). The splanchnic vascular bed representing the largest regional vascular conductance constitutes an important blood reserve (Escourrou *et al.* 1993) and is sensitive to baroreceptor stimulation. Thus, a low level of LBNP (≤ 20 mmHg) suffices to reduce splanchnic perfusion without changes in mean aortic pressure (Hirsch *et al.* 1989, Johnson *et al.* 1974). On the other hand, 50 mmHg of LBNP reduces splanchnic blood flow by more than 30% (Rowell *et al.* 1972) and reduces splanchnic vascular conductance by roughly the same percentage, by a rise in sympathetic activity (Brown *et al.* 1966).

In LBNP experiments the positioning of the seal separating the normo- and hypobaric zones of the body has varied widely: iliac crest, level of umbilicus, mid-abdomen, below the chest level, or may have not been reported. It is conceivable that varying sealing positions may affect the cardiovascular response. Using a seal around the iliac crest does not mechanically compress the bladder or the intestinal region and, therefore, does not compromise splanchnic blood flow (Brown *et al.* 1966). However, mesenteric hepatic blood flow, before and during LBNP, may be affected by increased abdominal pressure and the extent of compression of the splanchnic region caused by the location of the seal. An abdominal seal during LBNP compressing the abdominal region (Wasmund *et al.* 2003) could affect the circulation more than a seal positioned at the level of the iliac crest. Furthermore, external negative pressure applied to the abdomen would be expected to decrease central venous pressure, lung compliance, and airway pressure (Valenza *et al.* 2003).

In this study it was hypothesized that LBNP with UA sealing compresses the abdomen, provides suction on the splanchnic area, and creates a larger cardiovascular stress than does IC sealing. It was also investigated whether the sealing position itself influenced central blood volume as assessed by thoracic electrical impedance, and/or cardiovascular responses to LBNP as assessed by heart rate and hepatic perfusion.

Methods

To avoid effects of confounding variables such as height, gender, or athletic training on cardiovascular responses during LBNP (Goswami *et al*. 2008) we carefully selected 14 (25 ± 4 yr, 76 ± 8 kg, 1.75 ± 0.05 m, and 1.72 ± 0.15 m^2 body surface area) healthy, male volunteers of moderate physical fitness, free from cardiovascular, renal, and pulmonary diseases and not on any medication. Subjects abstained from use of tobacco, caffeine, alcohol, and heavy exercise for at least 48 h preceding each investigation and the subjects served as their own controls. The study protocol was approved by the Graz Medical University Research Ethics Committee and written informed consent was obtained from each subject. Before the study, LBNP sham runs without blood sampling were carried out for familiarization (Grasser *et al.* 2008, Laszlo *et al.* 1998).

Protocols were conducted between 9 and 12 a.m. to minimize circadian influences on hemodynamic variables (Gillen *et al.* 1994; Panza and Quyumi 1991) and were separated by 2 weeks. The subjects were fasting and emptied the bladder before each study. An antecubital vein was cannulated for blood sampling and administration of indocyanine green (ICG).

Experiments were carried out in a semi-dark and quiet room maintained at 24 ^{o}C and humidity at 55%. A padded pair of tightly connected chains was used to stabilize and maintain an exact sealing position (Fig 1). The box was equipped with a footrest that was individually adjusted before LBNP was commenced. A pillow supported the head to avoid stimulation of the otolith organs which has been reported to increase muscle sympathetic nerve activity and calf vascular resistance (Hume and Ray 1999).

LBNP was applied with the seal at either the UA or IC (Fig 1). The spine of the anterior superior iliac was the IC anatomical landmark; for the upper abdomen, the sealing level was at the lowest palpable rib in the mid-clavicular line, and therefore, included the splanchnic area in the region exposed to LBNP. Pressure within the box was lowered electronically by a pump within 10 s and monitored by an electronic gauge (Laszlo *et al.* 1998). LBNP (-40 mmHg) lasted for 15 min since longer periods have been shown to affect LBNP tolerance (Greenleaf *et al.* 2000). During LBNP, subjects were instructed to avoid movements of the lower limbs and to breathe normally.

Baseline data were collected for 30 min in the supine position, with the seal in place, to allow for re-equilibration of gravity-related fluid shifts (Hagan *et al.* 1978). Each LBNP protocol involved sealing at either IC or UA with 14 days between studies in randomized order. The time course of the experimental protocol is shown in figure 2.

Blood volume and hepatic perfusion

Twenty five mg of ICG were injected 20 min before LBNP. Transcutaneous ICG concentration was measured by the DDG-2001K Dye Densitometer (Nihon Kohden, Japan) using a nose probe and the initial hemoglobin concentration was measured by standard

techniques. Blood volume and hepatic blood flow were calculated from the amount of ICG injected and the measured ICG disappearance rate.

Plasma volume shifts

Plasma samples (0.2 mL) were prepared from heparinized blood and measured within an hour. Plasma volume changes were determined from changes in plasma mass density (PD; g L^{-1} at 37.0°C) measured with a DMA 602 MW (Paar KG, Graz, Austria) (Hinghofer-Szalkay 1986). Changes in plasma volume (PV%) were calculated from plasma density at baseline ($PD_{baseline}$) and at the end of LBNP (PD_{LBNP}):

$$PV\ \% = \frac{PD_{baseline} - PD_{LBNP}}{PD_{LBNP} - 1008} \times 100$$

where 1008 refers to the density of the filtered fluid (Hinghofer-Szalkay and Moser 1986).

Thoracic electrical impedance

For an estimate of changes in central blood volume, transthoracic electrical impedance was monitored (Task Force Monitor, CNSystems, Graz, Austria). Surface electrodes were placed at the neck and at the midclavicular line at the xiphoid process level (Fortin *et al.* 2006).

Hemodynamics

Blood pressure and heart rate were measured using a finger cuff (Finometer; Finapres Medical Systems, Arnhem, The Netherlands) and calibrated to standard arm cuff measurements. This

system also provides an estimate of cardiac stroke volume and is becoming increasingly used in physiological and clinical research (Schneditz *et al.* 2007).

Data analysis

Data are expressed as means ± S.E.M. Hemodynamic variables were averaged over 5 min windows preceding the start and end of LBNP, respectively. Hypothesis testing was carried out using two-way ANOVA with main effects of LBNP and sealing position. A probability $p<0.05$ rejected the null-hypothesis.

Results

Although blood volume at rest was not different between the two applied sealing positions (5.9 ± 0.3 L), resting values of liver perfusion and thoracic electrical impedance were different ($p<0.05$) (Table 1). Resting UA was characterized by lower thoracic impedance (26.9 ± 1.1 vs 29.0 ± 0.8 Ω, $p < 0.001$) and hepatic perfusion (1.6 vs 1.8 L min^{-1}, $p < 0.05$) compared to IC.

During LBNP, heart rate was greater during UA (80.6 ± 3.3 bpm) than IC (76.0 ± 2.5 bpm) ($p < 0.01$) and thoracic impedance increased more during UA (3.2 ± 0.2 Ω) than IC (1.8 ± 0.2 Ω) application ($p < 0.0001$). Stroke volume was reduced by 30% in UA and 25% in IC, but the difference did not reach significance ($p=0.1$). With both sealings, LBNP-induced effects remained unchanged for mean arterial pressure (-3.0 ± 1.1 mmHg), cardiac output (-1.0 L min^{-1}), and plasma volume (-11%).

Discussion

This study found that the position of the seal used for lower body negative pressure had important effects on cardiovascular variables, and that some differences were present before application of LBNP. More specifically, central blood volume, as indicated by increased thoracic electrical impedance, was reduced at rest when the seal was placed in the UA position with consequences for heart rate and splanchnic blood flow. Furthermore, when LBNP was applied there was a more pronounced increase in heart rate when the LBNP included the abdominal region.

Baseline thoracic impedance (Z_O) is inversely related to thoracic fluid volume (Pomerant et al. 1970) and central blood volume (Cai *et al.* 2000; Ebert *et al.* 1986). The pre-LBNP differences we observed can be interpreted as indications for fluid displacement with the simple placement of the UA seal that increased central blood volume. Tanaka *et al.* (1997) experimented with inflatable abdominal cuffs and observed a blood shift from the splanchnic to the thoracic region. Compression of the abdomen and limbs has also been shown to increase the effective circulating blood volume (Denq *et al.* 1997; Uemura *et al.* 1999). It is also plausible that stimulation of low threshold skin afferents and mechanical compression of abdominal adipose tissue may have modulated sympathetic neural outflow, but is more likely that the differences seen between the sealing positions were due to regional fluid shifts.

During LBNP, higher thoracic impedance, a larger reduction in splanchnic blood flow, and a larger increase in heart rate were observed with UA. This suggests a larger reduction in central blood volume (not only relative) and an increased sequestration of blood into lower body regions when the seal was located in UA position. This is in support of concomitant femoral vein distension and caval vein narrowing during compression of the abdomen (Smit *et al.* 2004). The larger heart rate response to LBNP with UA can be explained by a greater

reduction of cardiac preload, as indicated by the different degrees of thoracic impedance responses during LBNP. Cardiopulmonary receptors mediate LBNP effects (Furlan *et al.* 2001) with resulting tachycardia, reduced forearm as well as splanchnic blood flows. Pulse pressure changes, however, did not differ between UA and IC (Table 2). As the diastolic and systolic pressures were similar in both groups, we believe that the different heart rate response was driven by the different magnitude of cardiopulmonary receptor unloading (greater in UA than in IC).

The stability of arterial blood pressure was expected (Bevegard *et al.* 1977; Brown *et al.* 1966; Laszlo *et al.* 1998) at this level of LBNP as arterial blood pressure is maintained via both peripheral vascular resistance and heart rate adjustments (Kitano *et al.* 2005).

The LBNP-induced reduction in stroke volume was also expected (Ahmad *et al.* 1977; Laszlo *et al*. 1998; Stevens and Lamb 1965) but the effect was larger with UA than IC (see above). If attachment of the seal at UA itself caused an increased cardiac pre-load, it is conceivable that the elevated starting point of LBNP provided a larger volume reserve during the LBNP challenge, possibly allowing for a larger drop in stroke volume. This is in agreement with the larger stroke volume decrease we observed with UA sealing.

We observed a 15% decrease in cardiac output during LBNP, similar to that found by others (Berk *et al.* 1990; Stevens and Lamb 1965). Plasma volume loss with orthostatic stress occurs primarily in the lower limbs (Wolthius *et al*. 1970) and as both sealing locations had an equal effect on plasma density, it is conceivable that plasma volume loss was the same in UA and IC.

We used ICG clearance to assess hepatic flow before LBNP (Cherrick *et al.* 1960; Valenza *et al*. 2003) because application of the seal at the UA position might influence hepatic perfusion. At rest, before LBNP, hepatic perfusion was reduced by 11% with UA compared to IC. As most of the liver and spleen are protected by the ribcage, and may not have been directly compressed by the seal (except perhaps the lower right lobe of the liver), it is conceivable that the pressure generated by the seal below the ribcage was indirectly transmitted through the abdominal space to the liver thus affecting hepatic blood flow. However, the effect need not be direct. The likely reduction in central blood volume in itself increases sympathetic activity and reduces splanchnic blood flow (Brooksby and Donald 1971).

Thoracic impedance is affected by ventilation (Dowell *et al.* 1969). Application of the seal at UA could have caused differences in regional lung volumes (Frerichs *et al.* 2005) as well as in the depth of breathing (Furlan *et al.* 2001). In our study, hemodynamic data were obtained with the Finometer system. Finometer measurements correlate well with intra-arterial measurements of blood pressure (Imholz *et al.* 1990) and have been validated in subjects undergoing stress situations (Parati *et al.* 1989). Hemodynamic monitoring with the Finometer system has its own limitations since it may be affected by bias and drift and, therefore, relative changes in blood pressure were analyzed rather than absolute values (Lee *et al.* 2004). To avoid drift, we calibrated to absolute values from conventional cuff measurements on the contralateral upper arm every 15 min.

There are some limitations in this study. First, it cannot be ruled out that sympathetic neural activity was directly modulated by applying suction onto the abdominal area, in addition to cardiovascular reflex effects. It appears, however, that most likely the effects observed in this study resulted from the corresponding blood volume shifts (Cai *et al.* 2000; Ebert *et al.* 1986; Pomerant *et al.* 1970). It is also conceivable that the pressure applied at the sealing was not

always identical at each LBNP even in the same subject and this could have affected the results. Second, even though the effects of the seal were most likely mediated by changes in intra-abdominal pressures, intra-abdominal pressure was not measured in this study. While intravesical pressure may be a good surrogate for intra-abdominal pressure in the clinical setting, in this study one would have to measure small pressure changes in the upper abdomen which are not accessible by non-invasive and indirect means. Furthermore, thoracic impedance and ICG elimination are indirect measures, but they indicate thoracic fluid content, splanchnic flow and liver blood flow (Rowell *et al.* 1972) with sufficient reliability, and have been repeatedly used for this purpose in previous studies (Brown *et al.* 1966; Cai *et al.* 2000).

To summarize, LBNP sealing positions influenced hemodynamic responses to LBNP, and sealing attachment had an effect of its own. Liver blood flow and thoracic impedance were different between the two sealing locations pre-LBNP, an effect largely attributable to pressure exerted by the seal at these sites. During LBNP, a larger increase in heart rate was observed with UA, as opposed to IC, placement, secondary to a greater reduction in cardiac preload, as indicated by different degrees in thoracic impedance responses during LBNP as well as by the decrease in splanchnic blood flow.

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Conflict of interest

None.

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Table captions

Table 1: Effect of sealing position on hepatic perfusion and thoracic impedance (* refers to $p < 0.05$ between sealing positions).

Table 2: Hemodynamic and plasma density data (MAP: Mean arterial pressure; DBP: Diastolic pressure; SBP: Systolic pressure; PP: Pulse pressure; TPR: Total peripheral resistance; CO: Cardiac output; PD: Plasma density). Heart rate (HR) and thoracic impedance (Z_O) were significantly altered from 5 min pre-LBNP to the last 5 min of LBNP. Differences of normalized changes between UA and IC are given in figure 3. LBNP effects on cardiac output, peripheral resistance, pulse pressure and plasma density were all significant, but there was no difference between IC and UA. Arterial pressures did not change with LBNP, except for systolic blood pressure, which decreased by 8.4% in both conditions.

Table 1

Rest (pre-LBNP)			
	Blood volume (L)	Liver perfusion (L min^{-1})	Thoracic impedance (Ω)
IC	5.9 ± 0.3	1.8 ± 0.1	29.0 ± 0.8
UA	5.9 ± 0.2	1.6 ± 0.1 *	26.9 ± 1.1*

(* refers to $p < 0.05$ between sealing positions)

Table 2

	Pre LBNP		During LBNP	
	IC	UA	IC	UA
HR [bpm]	66.7 ± 2.3	66.8 ± 3.2	76.0 ± 2.5	80.6 ± 3.3*
SV [mL]	97.1 ± 5.8	99.1 ± 4.8	72.4 ± 4.8	70.2 ± 5.0
TI [Ω]	29.0 ± 0.8	26.9 ± 1.1*	30.8 ± 0.9	30.1 ± 1.1
MAP [mmHg]	97.4 ± 1.4	96.4 ± 2.1	94.2 ± 2.1	93.7 ± 2.0
DBP [mmHg]	78.7 ± 1.9	77.7 ± 1.9	79.6 ± 2.1	78.9 ± 2.1
SBP [mmHg]	130.8 ± 1.4	131.3 ± 2.3	120.2 ± 2.7	120.3 ± 2.0
PP [mmHg]	52.0 ± 2.0	53.8 ± 1.2	40.5 ± 2.1	41.4 ± 1.5
TPR [mmHg s mL^{-1}]	0.95 ± 0.07	0.91 ± 0.04	1.11 ± 0.08	1.05 ± 0.05
CO [L min^{-1}]	6.5 ± 0.4	6.5 ± 0.3	5.5 ± 0.4	5.5 ± 0.3
PD [g L^{-1}, 37.0°C]	1019.21 ± 0.13	1019.22 ± 0.17	1020.44 ± 0,13	1020.64 ± 0.23

(* refers to $p < 0.05$ between sealing positions)

Figure legends

Figure 1: Sealing at iliac crest (IC, left) and upper abdomen (UA, right panel) positions.

Figure 2: Experimental protocol. ICG: Indocyanine green injection. Blood was collected for plasma density (PD) measurements. Hemodynamic data were used from 5 min immediately preceding LBNP and from LBNP minute 10 to 15 (hatched areas).

Figure 3: Heart rate and thoracic impedance changes during LBNP application. Values are relative to pre-LBNP.

Figure 1

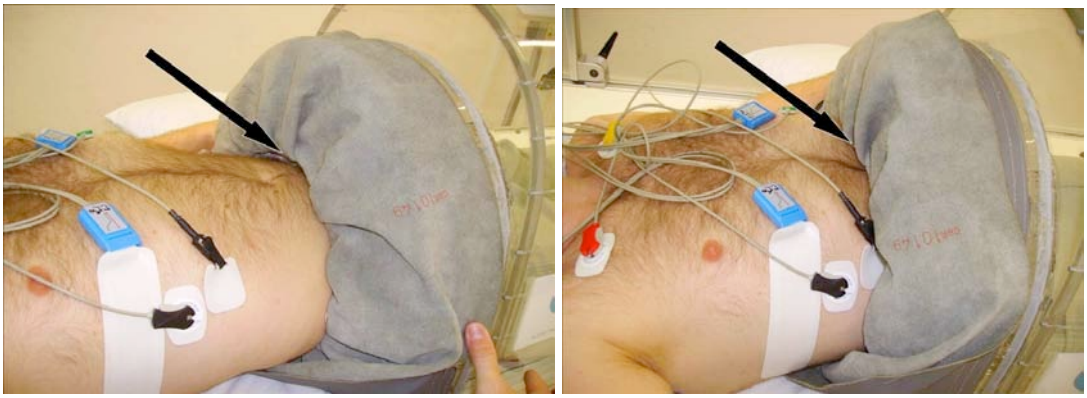


Figure 2

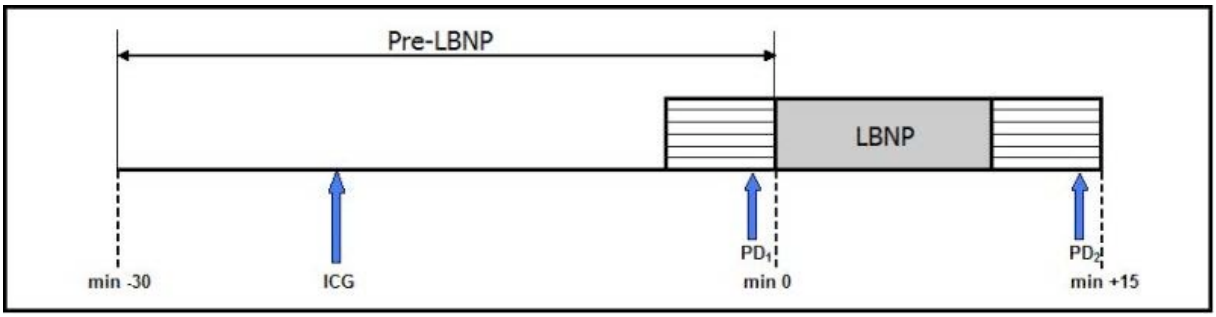
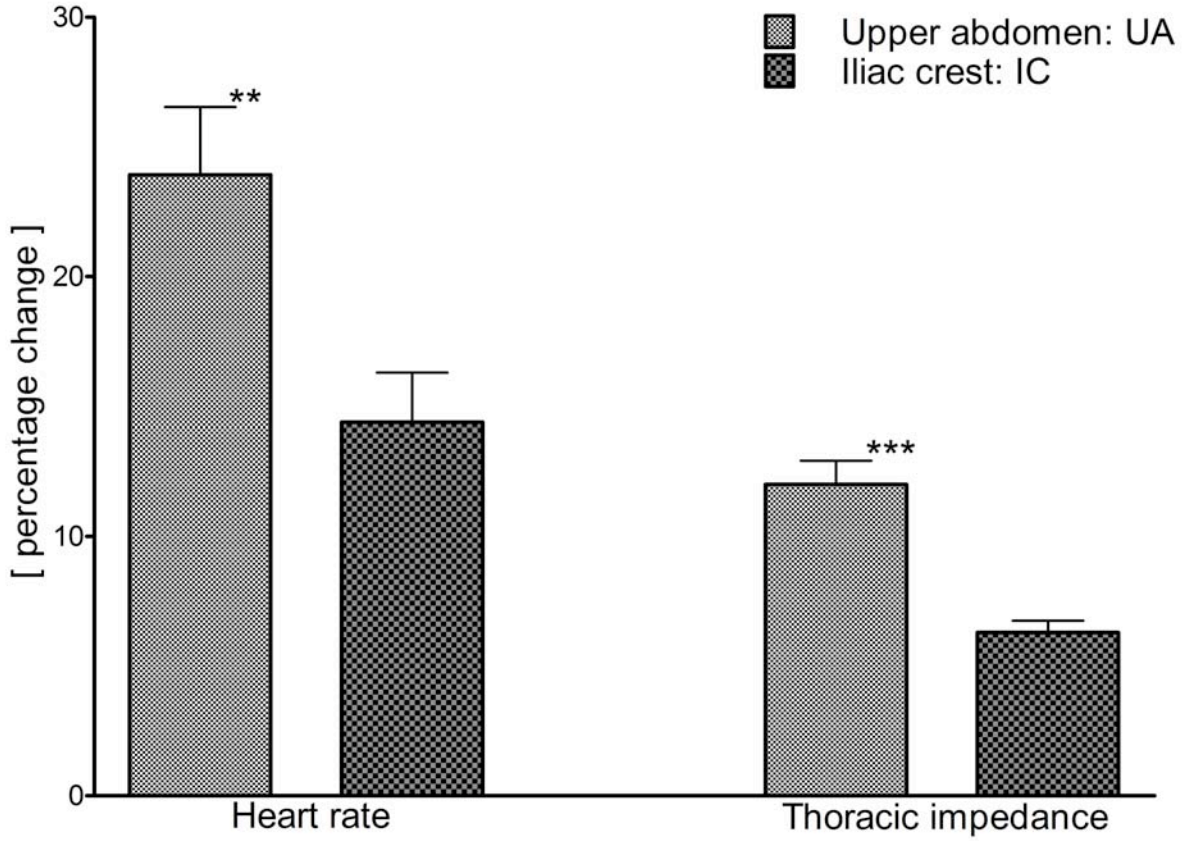


Figure 3


30
20
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**
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Upper abdomen: UA
Iliac crest: IC
Heart rate
Thoracic impedance