Left atrial distension and antioorthostatic decrease in arterial pressure and heart rate in humans

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Left atrial distension and antioorthostatic decrease in arterial pressure and heart rate in humans. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2632–H2638, 1997.—It was investigated to what degree left atrial distension augments the hypotensive effects of a 15-min moderate antioorthostatic maneuver in humans. Ten healthy males underwent a posture change from upright seated (Seat, legs horizontal) to supine (Sup) or to supine with simultaneous lower body negative pressure (Sup + LBNP) to keep left atrial diameter (LAD) unchanged. After 2.5 min of Sup, mean arterial pressure (MAP) decreased from 94 ± 3 to 86 ± 3 mmHg (P < 0.05), whereas a similar decrease was delayed 7.5 min into Sup + LBNP. Heart rate (HR) decreased within 2.5 min of Sup from 68 ± 2 to 60 ± 3 beats/min (P < 0.05) and remained significantly decreased for at least 2.5 min longer than during Sup + LBNP. Aortic systolic distension (ASD) increased by 59 ± 17% during Sup (P < 0.05) but was unchanged during Sup + LBNP. The 29 ± 4% decrease in plasma norepinephrine (NE) during Sup (P < 0.05) was abolished during Sup + LBNP. In conclusion, the increases in LAD and ASD seem important stimuli for the prompt decrease in MAP, the 2.5-min longer-lasting decrease in HR, and the sustained decrease in NE during a 15-min moderate antioorthostatic posture change in humans.

MATERIALS AND METHODS

Ten male subjects [age 23.6 ± 0.6 yr (mean ± SE), height 182 ± 2 cm, and weight 76 ± 2 kg] completed the experiment. All were nonsmokers, had a negative history of cardiovascular and kidney diseases, and were healthy as indicated by a normal physical examination, hematocrit, arterial blood pressure, electrocardiogram (ECG), and urine test for glucose, leukocytes, erythrocytes, and protein. None of the subjects took any medication at least during the week before the study. Informed consent was obtained after the subjects had read a description of the experimental protocol, which was approved by the Ethics Committee of Copenhagen (KF 01–347/93) and in compliance with the declaration of Helsinki. No complications occurred.

Each subject spent the night at the laboratory, fasted for 12 h before the experiment, and was awakened at 7:30 AM on the day of study. Between 7:30 and 7:45 AM, the subjects went to the bathroom and walked one floor down to the experimental room. A short catheter (Venflon 2, 1.2 mm, length 45 mm) was then placed in a cubital vein for blood sampling. Thereafter, the subject was seated (Seat) with his trunk vertical with back and neck support and with the legs placed horizontally in an oblong box for LBNP. He was instrumented with electrodes for ECG recordings and cuffs (index finger and upper arm) for determination of arterial pressures and thereafter rested in this position for 1 h before start of the experiment.

As depicted in Fig. 1, the protocol consisted of two parts, A and B, with the sequence performed in a balanced, randomized order between the subjects and separated by 45 min of Seat, also with the legs placed horizontally in the LBNP box. The idea behind the two sessions was, in session A, to observed that low- and high-pressure receptors interact and that stimulation of low-pressure receptors attenuates the sensitivity of the arterial receptors.

To investigate to what extent left atrial distension contributes to the more prolonged adaption of MAP, HR, and NE to a sustained (15 min) moderate antioorthostatic maneuver, we introduce a new model in this study. The model includes a posture change from the upright seated (Seat, trunk vertical, legs horizontal) to the horizontal supine position (Sup) combined with lower body negative pressure (LBNP) to maintain left atrial diameter (LAD) unchanged. The hypothesis was tested that cardiopulmonary low-pressure receptors significantly contribute to the more prolonged (minutes) decrease in MAP, HR, and NE during a moderate antioorthostatic maneuver. Furthermore, we hypothesized that, with this model, the quantitative contribution of the low-pressure receptors on the cardiovascular adaptation to an antioorthostatic maneuver could be determined.

AN ANTIORTHOSTATIC POSTURE change from upright seated to 3° head-down tilt induces a decrease in mean arterial pressure (MAP), heart rate (HR), and central venous plasma concentration of norepinephrine (NE) in humans. The decrease in MAP is maintained for at least 1 h and the decrease in HR and NE for at least 12 h (22). The mechanisms for the decrease in MAP, HR, and NE probably involve a combined stimulation of cardiopulmonary low-pressure and arterial high-pressure receptors. The relative contribution of each type of receptor, low vs. high, is, however, not clear at present (2, 6, 17, 18, 29).

Numerous investigators have studied the mechanisms of immediate cardiovascular responses to changes in baroreceptor stimulation in humans using a host of maneuvers (26). Parati et al. (24) and Shi et al. (30) observed that increased cardiopulmonary receptor activity reduces the arterial baroreceptor sensitivity regarding control of HR. Correspondently, Pawelczyk and Raven (25) concluded that reduction in central venous pressure augments HR and arterial pressure responses to carotid baroreceptor stimulation. Thus these authors observed that low- and high-pressure receptors interact and that stimulation of low-pressure receptors attenuates the sensitivity of the arterial receptors.

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simultaneously increase LAD and carotid sinus pressure by changing position from Seat to Sup and, in session B, to maintain LAD unchanged during the same changes in posture by simultaneous application of LBNP (Sup + LBNP). Each part, A and B, lasted 45 min with 15 min of Seat (Seat-1), 15 min of Sup with (Sup + LBNP) or without (Sup) application of LBNP, and finally 15 min of Seat (Seat-2). LBNP was initiated just before the subject was passively tilted from Seat-1 to Sup + LBNP by tilting the back support to the horizontal position. The subjects briefly used their arm muscles to push themselves into the appropriate supine position so that the iliac crest was at the opening of the LBNP box when going from Seat-1 to Sup or from Sup + LBNP and back to Seat-2. The LBNP level was manually adjusted to keep LAD unchanged compared with that of Seat-1 as estimated by simultaneous measurements by M-mode echocardiography. In this way, we aimed at keeping the stimulation of left atrial low-pressure receptors unchanged during session B. Arterial pressure determinations, blood sampling, and echocardiography were performed simultaneously at either 2.5 (arterial pressures)- or 5-min intervals.

LBNP was carried out in an airtight Plexiglas box connected to a vacuum cleaner. The box surrounded the subject from the iliac crest and down and was attached to the subject by a plastic sheet fastened with a belt just above the iliac crest. A stable level of LBNP was obtained within a maximum of 30 s at approximately 25 mmHg, and it thereafter fluctuated between 17 and 33 mmHg. The fluctuations were caused by continuous manual adjustments of LBNP, so that LAD was kept unchanged. It should be noted that in this experiment the LBNP was effective from a lower level on the body than in previous studies (20, 21), since the LBNP box had been modified with a larger opening and a wider plastic sheet connecting subject with box to facilitate the posture changes. Therefore, during LBNP, the sheet was pressed inward through the opening making LBNP effective from somewhere below the iliac crest and down. In session A, the vacuum cleaner was turned on as in session B but disconnected from the LBNP box so that the subject would experience the same level of noise.

Systolic (SAP) and diastolic (DAP) arterial pressures were measured in the brachial artery by automatic oscilometry on the upper right arm (Propaq 102, Damesca, Denmark). This equipment has previously been tested against invasive brachial arterial pressure measurements (9). Arterial pulse pressure (PP) was calculated from SAP minus DAP and MAP from DAP + ⅓PP. In addition, SAP, DAP, and MAP were measured by a photoplethysmographic method (Finapres, 2300 Finapres, Ohmeda) in the left index finger with the pressure signal recorded on a strip-chart recorder (Gould ES 1000), and MAP was estimated as the electronic mean. The brachial and finger cuffs were kept at level with the midaxillary line when the subject was Sup and at level with the fourth intercostal space during Seat. To improve accuracy and since MAP can be considered the same in the finger and upper arm, respectively, MAP is presented as the mean value of the two methods (7).

To calculate MAP at the level of the carotid sinus (CSP) during Seat, the hydrostatic column from the level of the fourth intercostal space to the thyroid cartilage was subtracted from the MAP values measured at heart level (6). HR was measured at 2.5-min intervals and calculated over 1-min periods from ECG recordings registered by electrodes on the chest and connected to an oscilloscope (Diascope DS 521, S and W) and a strip-chart recorder (Gould ES 1000).

LAD was measured according to the criteria of Feigenbaum (8) at 5-min intervals during end expiration as an average of measurements from three M-mode pictures (printouts from a video recorder, Sony SVO-9500 MDP) obtained from the parasternal long-axis view by echocardiography (Aloka SSD 500, Simonsen and Weel). On the same printouts, the aortic diameters just above the valves were measured at end systole and diastole, and aortic systolic distension (ASD) was calculated as the systolic minus diastolic diameter (14). The measurements were performed in a blind fashion.

Blood (17 ml) was sampled at 5-min intervals and immediately transferred into various chilled tubes. The catheter was thereafter flushed with 15–20 ml of isotonic saline. Samples for determination of concentrations of plasma NE and plasma epinephrine (E) were transferred to polyethylene tubes containing 20 µl/ml blood of a mixture of reduced glutathione (0.195 M) and ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA; 0.250 M) adjusted to pH 6–7 with NaOH. The samples were immediately placed on ice and subsequently centrifuged at 4°C at 1,500 g for 10 min. Plasma was thereafter transferred to polyethylene tubes and frozen at −30°C for later analysis by a radioenzymatic assay (16).

The tubes for determination of plasma concentration of arginine vasopressin (AVP) contained 1.5 mg K 2EDTA/ml blood, and those for determination of plasma renin activity (PRA) and plasma osmolality contained 15 ± 2.5 U Li-ion-
Results

Cardiovascular responses. LAD increased during Sup compared with the mean value of Seat-1 from 28.9 ± 0.6 mm to a maximum of 31.9 ± 0.6 mm (P < 0.05) and returned to the levels of Seat-1 during Seat-2 (Fig. 2). During Sup + LBNP, LAD did not change compared with values of Seat and varied nonsignificantly between 28.2 ± 0.6 and 29.6 ± 0.9 mm (Fig. 2).

ASD increased during Sup compared with the mean value of Seat-1 from 1.8 ± 0.3 to a maximum of 2.6 ± 0.4 mm (P < 0.05). There was no significant change during Sup + LBNP compared with that of Seat (Table 1). The end-diastolic aortic diameter did not change during any of the procedures and varied insignificantly between 29.5 ± 0.5 and 30.1 ± 0.9 mm.

MAP decreased from a mean value of 93 ± 3 during Seat-1 to a nadir of 86 ± 3 mmHg within the initial 2.5 min of Sup (P < 0.05) and remained at this level during the remainder of the period. During the initial 5 min of Sup + LBNP, MAP did not change significantly compared with that of Seat-1. Thereafter, MAP decreased gradually and attained the same level as that of Sup during the subsequent 10 min. MAP returned to the level of Seat-1 during Seat-2 within 2.5 min after Sup and Sup + LBNP (Fig. 2). PP did not change significantly during any of these procedures. DAP in the index finger (Finapres) decreased from a mean value of 79 ± 3 during Seat-1 to a nadir of 69 ± 3 mmHg during Sup (P < 0.05), remained at this level, and returned within 2.5 min of Seat-2 to that of Seat-1. DAP in the finger did not change during Sup + LBNP compared with that of Seat varying insignificantly between 73 ± 3 and 77 ± 2 mmHg (Table 1).
HR decreased promptly during Sup from a mean value during Seat-1 of 67 ± 2 to a nadir of 60 ± 3 beats/min within 2.5 min and remained at this level throughout the subsequent 2.5 min (P < 0.05). Thereafter, there was no significant difference from the values of Seat. During Sup + LBNP, HR decreased from a mean value during Seat-1 of 68 ± 2 to a nadir of 62 ± 3 beats/min within 2.5 min (P < 0.05) and returned to the level of Seat after 5 min. Thus HR was above that of Seat-1 Sup from between 2.5 to a nadir of 60 ± 3 beats/min within 2.5 min and returned to the level of Seat after 5 min. Thus HR was above that of Seat after 5 min. Therefore, during Sup + LBNP, HR decreased from a mean value of 182 ± 12 to a nadir of 120 ± 11 pg/ml after 10 min (P < 0.05). Plasma NE was similar to that of Seat-1 during Sup + LBNP (Table 2). Plasma concentration of E decreased during SUP compared with that of Seat-1 but temporarily increased after 5 min from a mean value of 169 ± 12 to 209 ± 10 pg/ml (P < 0.05). The subsequent values during Sup + LBNP were similar to those of Seat-1. During Seat-2, plasma NE was similar to that of Seat-1 except for a temporary increase that occurred 5 min into Seat-2 (P < 0.05, Fig. 3).

Endocrine responses. When the subjects were tilted from Seat-1 to Sup, plasma concentration of NE decreased from a mean value of 182 ± 12 to a nadir of 120 ± 11 pg/ml after 10 min (P < 0.05, Fig. 3). Plasma NE returned to the level of Seat-1 5 min into Seat-2. During Sup + LBNP, plasma NE did not decrease compared with that of Seat-1 but temporarily increased after 5 min from a mean value of 169 ± 12 to 209 ± 10 pg/ml (P < 0.05). The subsequent values during Sup + LBNP were similar to those of Seat-1. During Seat-2, plasma NE was similar to that of Seat-1 except for a temporary increase that occurred 5 min into Seat-2 (P < 0.05, Fig. 3).

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Additional methodological study. LAD measured in M mode from the parasternal long-axis view increased from Seat-1 to Sup from between 27.7 ± 0.7 and 28.4 ± 0.6 to a maximum of 31.6 ± 0.5 mm (n = 5, P < 0.05). During Sup + LBNP, LAD did not change compared with that of Seat, and varied nonsignificantly between 28.1 ± 0.6 and 28.9 ± 0.8 mm (n = 5). The values of LAD measured in two dimensions from an apical four-chamber view exhibited the same pattern. From Seat to Sup there was an increase from between 31.8 ± 1.4 and 32.2 ± 1.6 to a maximum of 35.7 ± 2.0 mm (n = 5, P < 0.05), whereas LAD varied insignificantly between 31.6 ± 1.6 and 32.7 ± 1.5 mm during Seat and Sup + LBNP (n = 5).
The initial increase in CSP was greater when the subjects were tilted from Seat to Sup + LBNP than from Seat to Sup. The simultaneous decrease in HR was, however, of smaller magnitude (Fig. 2). It is noteworthy that the decrease in HR during the posture change from Seat to Sup + LBNP did not induce a decrease in MAP within the initial 5 min. Furthermore, the decrease in MAP, which lasted from the 7.5th to 15th min of Sup + LBNP, occurred despite a return of HR back to that of Seat after 5 min (Fig. 2). Therefore peripheral vasodilatation probably induced the decrease in MAP during Sup + LBNP.
The decrease in peripheral DAP in the index finger during Sup indicates that peripheral vasodilation and suppression of HR are two mechanisms by which the low-pressure receptors protect the brain against pressure increases during an antiorthostatic posture change. These responses were attenuated or abolished during Sup + LBNP. Because DAP in the finger was unaffected during Sup + LBNP compared with that of Seat, the decrease in MAP could have been accounted for by vasodilation in other vascular beds than that presented in the finger.

Forearm venous concentration of NE decreased during the posture change from Seat-1 to Sup. During Sup + LBNP, however, this decrease did not occur, suggesting that forearm sympathetic nervous activity (SNA) is unaffected by changes in CSP. These results therefore indicate, in agreement with results of other investigators, that low-pressure reflexes (LAD) govern the NE release in the forearm (10, 11, 23, 28).

The decrease in MAP despite a lack of reduction in NE during Sup + LBNP might have been caused by reduction in efferent SNA to organs and compartments other than the forearm. It has been observed that an increase in SNA to muscles in the forearm during LBNP does not affect SNA to skin of the same region (32). Thus, even though NE in forearm venous blood is unchanged, this does not exclude that efferent SNA to other regions was in fact decreased, causing peripheral vasodilation and a decrease in MAP. Furthermore, small changes in SNA may not necessarily be reflected in NE of forearm venous blood. Therefore a minor decrease in SNA, which might not have been detectable by our methods, could also have occurred in the forearm.

The increase in NE, 5 min into Sup + LBNP and 5 min into Seat-2, is not readily explicable. Theoretical considerations suggest that the posture change per se could have induced some degree of muscle activity in the upper extremities, resulting in a temporary increase in release of NE, or that the posture change per se induced a temporary decrease in metabolic clearance of NE. It is also possible that adjusting the level of LBNP immediately after the posture change was not totally successful and thus resulted in a temporary decrease in LAD compared with that of Seat-1. That such an initial temporary “overshooting” of LBNP was the cause for the increase in NE is unlikely, since we observed the same temporary increase in NE in another study, in which a lower level of LBNP was applied so that LAD was increased when going from Seat to Sup + LBNP (n = 6, unpublished observations). The temporary increase in NE when posture is changed therefore seems independent of LBNP.

In this study, we did not detect a significant decrease in plasma AVP during the posture change from Seat-1 to Sup or to Sup + LBNP. It is noteworthy, however, that the lowest AVP values were observed during Sup and Sup + LBNP and that they did not differ significantly.

PRA was higher during Sup + LBNP than during Seat-1. This was an unexpected finding and indicates that the increase in this variable above the level of Seat was induced by means other than changes in stimulation of baroreceptors. Because it is known that renal SNA and NE directly stimulate release of renin (29), the increase in NE 5 min into Sup + LBNP could account for the increase in PRA. It is well known that the renin response usually is delayed (21, 29). Therefore, more prolonged interventions are necessary to investigate the effects of posture on PRA.

It could be argued that the decrease in plasma NE during the posture change was partly caused by the fluid shift from the interstitial to the intravascular space, due to difference in concentration of NE in blood and tissue fluid. Because a posture change, however, from Seat to head-down tilt (6°) causes hemodilution of a maximum of 10% (L. B. Johansen, R. Videbaek, M. Hammerum, and P. Norsk, unpublished observations) and the concentration of hormones in the interstitial space is far from zero (12), hemodilution cannot at all account for the changes of the posture change in the present study.

Possible limitations in interpreting the results. In the present study, we chose to measure LAD by echocardiography to monitor changes in stimulation of left atrial receptors. It cannot be excluded that even though LAD was prevented from increasing, the left atrial and cardiopulmonary low-pressure receptors were in fact stimulated. This is, however, unlikely, since we observed the same direction of changes in LAD when measured in two different planes in an additional study. Thus the probability of an asymmetric change in the shape of the left atrium is low.

Even though it is likely that changes in ASD, as measured by M-mode echocardiography, accurately reflect changes in stimulation of aortic receptors, this notion remains to be determined. Furthermore, it should be noted that MAP was estimated as the mean of values in the brachial artery and the index finger. It is, however, not known whether the changes in MAP in the central aorta are similar to the more peripheral ones that we obtained.

It is a theoretical possibility that reflexes elicited from receptors in the abdominal area caused by altered intra-abdominal pressure during posture changes combined with LBNP could account for some of the responses (4). If this were the case, the maintenance of the unchanged LAD and ASD might not have been the only mechanisms for the attenuated MAP, HR, and NE responses. Furthermore, vestibular, ocular, or tactile stimuli during the changes in posture could theoretically have also played a role. These notions remain speculative but should be considered in future investigations.

In conclusion, maintaining LAD and consequently ASD unchanged during a posture change from Seat to Sup attenuates the decrease in MAP and HR and abolishes the decrease in NE. Thus changes in LAD and ASD seem important stimuli for the prompt decrease in MAP, the 2.5-min longer-lasting decrease in HR, and the sustained decrease in NE during a moderate antioorthostatic posture change in humans. Furthermore, the
results indicate that NE release to forearm venous blood is independent of changes in CSP. We suggest the present model be used to investigate interactions of cardiopulmonary low- and arterial high-pressure receptors on cardiovascular, endocrine, and renal variables in humans during more long-term (minutes to hours) interventions.

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