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ORIGINAL ARTICLE

Environmental stress and vestibular inputs modulate cardiovascular responses to orthostasis in hypertensive rats

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The frequent accompaniment of hypertension by orthostatic circulatory disorders prompted us to investigate the effect of repeated and sustained head-up and head-down tilt positions on cardiovascular responses in spontaneously hypertensive rats *vs.* Wistar rats using radiotelemetric implants. Repeated orthostasis caused a transient elevation in blood pressure (7.3 ± 1.7 mmHg) and heart rate (39.7 ± 10.5 BPM), while repeated antiorthostasis led only to reversible tachycardia (85.6 ± 11.7–54.3 ± 16.8 BPM) in spontaneously hypertensive rats. In contrast to the Wistar rats, sustained tilt failed to affect the blood pressure or heart rate in spontaneously hypertensive rats because the environmental stress of being placed in horizontal tilt cages prior to the sustained tilt test induced marked changes in cardiovascular parameters. Non-specific stress responses were eliminated both by the anxiolytic diazepam and a sub-anesthetic dose of chloralose. Unlike diazepam, chloralose amplified the orthostatic pressor responses in the Wistar rats. In contrast to diazepam preventing the pressor response and associated tachycardia in spontaneously hypertensive rats, chloralose elicited this effect during both sustained orthostasis (36.0 ± 7.3 mmHg, 63.7 ± 21.8 BPM) and antiorthostasis (42.9 ± 10.9 mmHg, 82.8 ± 25.4 BPM), with a reduced baroreflex sensitivity. However, during sustained orthostasis, removal of the vestibular input led to a depressor response with bradycardia (12.5 ± 3.2 mmHg, 59.3 ± 17.3 BPM), whereas antiorthostasis only reduced blood pressure (20.5 ± 7.1 mmHg) in the spontaneously hypertensive rats. We conclude that repeated tilts induce a transient pressor response and/or tachycardia in spontaneously hypertensive rats. Cardiovascular parameters are suppressed by diazepam, whereas chloralose evokes both blood pressure and heart rate responses during sustained tilts, which are primarily elicited by baroreflex suppression in hypertension. Vestibular inputs support cardiovascular tolerance to sustained postural changes in a rat model of human 'essential' hypertension.
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INTRODUCTION

Hypertension has elements of polygenic and multifactorial origins[1,2] that lead to an increase in diverse circulatory and renal complications.[1,3–6] Due to high and increasing prevalence, hypertension poses a major public health challenge[3–5,7] with pathophysiological mechanisms in its initiation and maintenance being coupled to diabetes, autonomic disorders, aging and drug treatments. Such challenges are also noted with orthostatic changes in various circulatory disorders.[8]

Active standing and head-up tilt tests (alone or together with ambulatory blood pressure recording) have become useful tools for detecting orthostatic disorders as diagnostic or prognostic indicators of human hypertension.[9–16] We developed tilt cages to keep conscious rats in a 45° head-up tilt position (Figure 1) in which saphenofemoral venous blood pressure doubles,[17] thus allowing the study of local orthostatic adaptation mechanisms.[18] The tilt technique was combined with telemetry to investigate systemic cardiovascular responses. In these studies, normotensive Wistar rats exhibited sustained blood pressure (BP) elevation from head-up and head-down postural challenges due to sympathetic activation.[19,20] Pressor responses were augmented by a reduction in non-specific stress but remained unaffected by an elevation in baseline BP with systemic inhibition of nitric oxide synthesis using N(G)-Nitro-L-arginine methyl ester.[19,20] This response was suppressed by vestibular lesioning[21] and orthostasis and was accompanied by a reduced spontaneous baroreflex sensitivity.[20,22]

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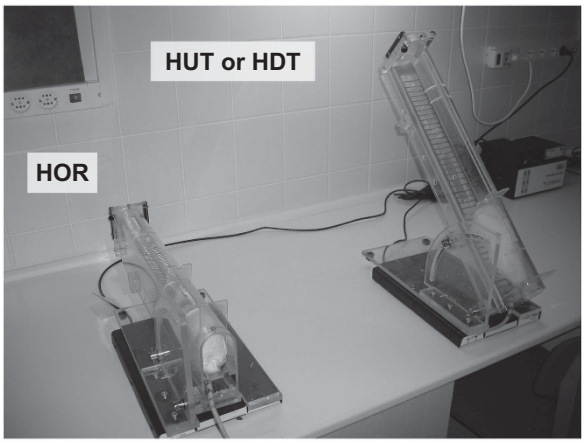

Figure 1 Cardiovascular effects of orthostatic and antiorthostatic body positions on SHRs were investigated in tilt cages used for positioning the animals from horizontal (HOR; left) to either a 45° head-up tilt (HUT) or a 45° head-down tilt (HDT) position (right).

Orthostatic cardiovascular disorders may contribute to elevated BP or may be consequences of a hypertensive state in humans. For example, extreme dipper and nondipper elderly hypertensive patients are more frequently diagnosed with orthostatic hypertension and hypotension, respectively.[12] Orthostatic hypertension is also associated with masked hypertension in apparently healthy subjects.[9] Consequently, to better understand the orthostatic adaptation mechanisms in hypertension, we compared the initial cardiovascular responses to non-specific stress and subsequent orthostatic responses to repeated brief and sustained periods of head-up and head-down stressors in spontaneously hypertensive rats (SHRs) to those in Wistar rats during the light period of their diurnal cycle. As the SHR strain exhibits cardiovascular hyper-reactivity to stress,[23–27] we postulated that postural changes would result in augmented cardiovascular responses in an established hypertension model, such as the SHR. Based on our earlier results,[19,20] postural responses are also supposed to be modulated by environmental stressors in hypertension, because pre-existing non-specific stress levels can critically influence the response to a specific orthostatic stressor. Thus, anxiolytic diazepam and sub-anesthetic chloralose were administered to eliminate existing environmental influences prior to tilt tests. Because orthostatic tolerance is supported by the vestibular inputs in rats[21,28] and humans,[15,29] their potential role in hypertension was also investigated by performing a labyrinthectomy. Finally, the mechanism determining the responses was also related to the spontaneous baroreflex sensitivity and spectral heart rate (HR) variability.

METHODS

Experimental animals

We used adult male SHRs (Harlan, Germany, $n=8$) and Wistar rats (Harlan, Germany, $n=11$) that were individually housed with 12-h light (07^{00}–19^{00}) and dark (19^{00}–7^{00}) cycles. The studies were approved by the Semmelweis University Committee on the Ethical Use of Experimental Animals (590/99 Rh).

Surgery

Radiotelemetric implants (Data Sciences International, St Paul, MN, USA) that measure aortic BP, HR, body temperature and locomotor activity were surgically implanted into rats as described previously.[19,20,30]

Experimental protocols

Control data were recorded with animals in traditional and in horizontal tilt cages (Figure 1). Orthostatic or antiorthostatic tilt was achieved by positioning the cages either into a 45° head-up tilt or a 45° head-down tilt position (Figure 1), respectively, which was maintained either for a 5-min duration with a 5-min pause that was repeated three times each (repeated tilt) or for 120 min (sustained tilt). To examine the effect of the sustained horizontal position, rats were maintained in the horizontal tilt cages for 120 min.

Drug administration

Chloralose (26 or 43 mg kg^{-1} bw i.p., Sigma, St Louis, MO, USA) and diazepam (5 mg kg^{-1} bw p.o., Gedeon Richter Plc., Budapest, Hungary) were administered at the end of the control period in order to reduce the level of stress preceding the sustained tilt procedures.

Vestibular lesion

We used a combined microsurgical-chemical technique for labyrinthectomy,[21,31] as described by Matsuda *et a.*[32]

Baroreflex sensitivity and sympathovagal balance

Spontaneous baroreflex sensitivity was calculated from the spontaneous fluctuations in BP and HR.[33] The power spectrum of HR variability that was calculated from continuous BP recordings was divided into low-frequency (LF, 0.04–1 Hz) and high-frequency (HF, 1–3 Hz) ranges, which were used to estimate sympathovagal balance.[34]

Statistical analysis

Values for the light and the dark phases, changes relative to horizontal values and mean ± s.e.m., were calculated from individual data points. Light and dark phases were compared using paired *t*-tests. One-way ANOVAs with repeated measures and Dunnett's pair-wise multiple comparisons were used to test differences from horizontal values. $P<0.05$ was considered statistically significant.

RESULTS

Diurnal rhythm

BP, HR, body temperature and locomotor activity as well as LF/HF ratio and spontaneous baroreflex sensitivity in SHRs showed regular diurnal rhythms in the traditional cages during the 24-h observation period (Figure 2), as seen in normotensive Wistar rats.[19,35] Average BP, HR, body temperature and locomotor activity significantly increased during the dark phase (light/dark, BP: 145.9 ± 5.3/154.4 ± 4.9 mmHg; HR: 276.4 ± 5.7/311.6 ± 9.6 BPM; body temperature: 37.3 ± 0.2/37.9 ± 0.2 °C; locomotor activity: 123.7 ± 8.1/268.6 ± 38.8 counts h^{-1}). LF/HF ratio increased (2.34 ± 0.16/2.72 ± 0.20) and spontaneous baroreflex sensitivity decreased (1.23 ± 0.11/1.02 ± 0.09 ms mmHg^{-1}), while LF (27.52 ± 6.12/20.86 ± 2.63 ms^2) and HF (13.34 ± 3.09/8.93 ± 1.38 ms^2) did not change in the dark phase (light *vs.* dark values, respectively).

Repeated tilts

BP and HR measurements in SHRs during the horizontal position in the tilt cage, which were recorded preceding the repeated orthostatic or antiorthostatic challenges, were significantly elevated compared to the home cage values for SHRs (Table 1). Repeated head-up tilt caused a significant elevation in both BP (cycle 1: +7.3 ± 1.7 mmHg and cycle 2: +4.9 ± 1.2 mmHg) and HR (cycle 1: +39.7 ± 10.5 BPM) early in the test, followed by BP and HR normalization (Figure 3a). Repeated head-down tilt caused reversible increases in the HR (cycle 1: 85.6 ± 11.7 BPM, cycle 2: 60.7 ± 19.7 BPM and cycle 3: 54.3 ± 16.8 BPM) without significantly affecting BP (Figure 3a). Body temperature rose when animals were placed in the horizontal tilt cage

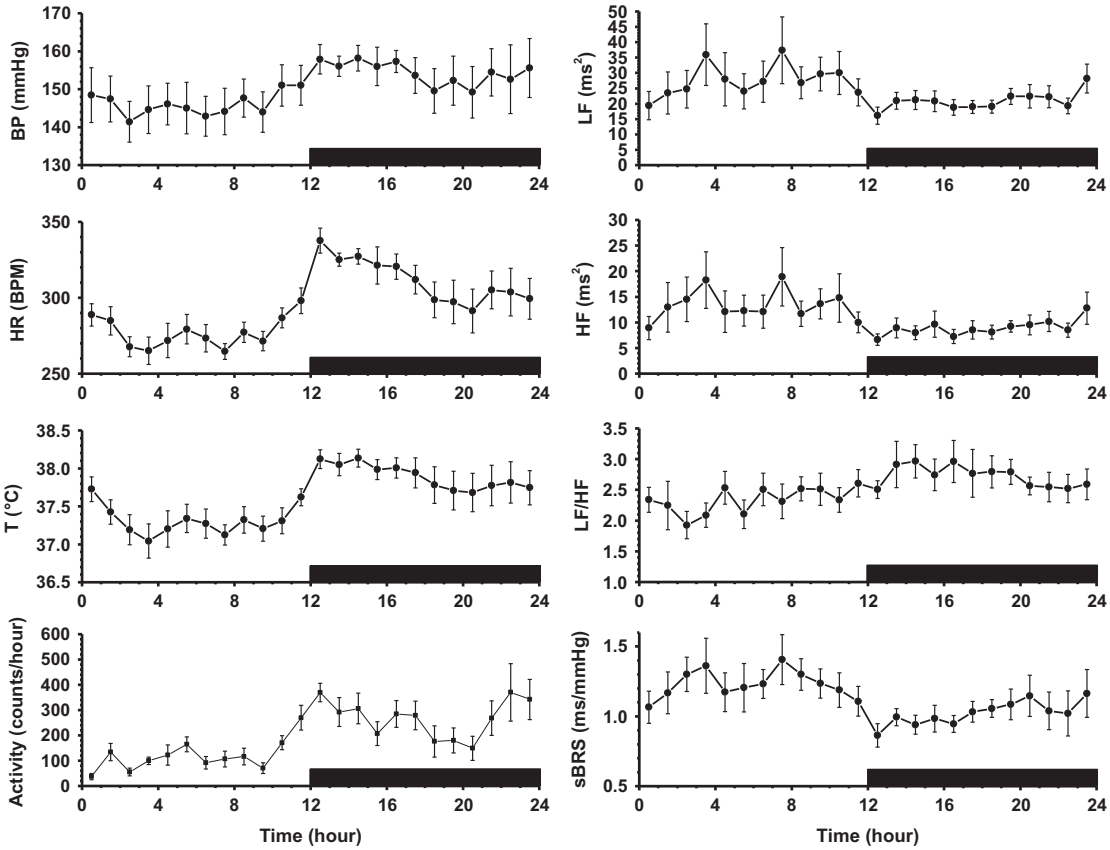

Figure 2 Diurnal variations in arterial BP, HR, body temperature (T) and locomotor activity (left) as well as in LF and HF components of the power spectrum of heart rate variability, their ratio (LF/HF) and spontaneous baroreflex sensitivity (sBRS, right) in SHRs. The dark phase of the 24-h observation period is indicated by filled bands ($n=8$).

(data not shown) and continued to increase during repeated tilt tests (Figure 3a).

Sustained tilts

Cardiovascular parameters were also significantly elevated in the horizontal tilt cages prior to the sustained tilt tests in both SHRs and Wistar rats (Table 1). Neither sustained horizontal nor head-up tilt nor head-down tilt caused a significant elevation in BP or HR in SHRs except at the very beginning of the latter test (Figure 3b). Body temperature was also elevated in the horizontal body position (data not shown), but only the antiorthostatic test elicited a further rise in body temperature (Figure 3b).

None of the spectral parameters or the spontaneous baroreflex sensitivity were altered in the sustained horizontal position in SHRs (data not shown). Spontaneous baroreflex sensitivity decreased during sustained head-up tilt that was accompanied by a reduction in the LF and LF/HF ratio (Figure 4a). With the sustained head-down tilt, reductions in spontaneous baroreflex sensitivity and LF were observed only at the very beginning of the test (Figure 4b).

In contrast, sustained orthostasis induced a steady BP elevation without tachycardia in Wistar rats (Figure 3c).

Effect of diazepam

Diazepam treatment prevented the initial rise of BP, HR (Table 1) and body temperature (data not shown) in the horizontal body position preceding both orthostatic and antiorthostatic tests in SHRs. Tilting did not influence BP or HR, but tilting did increase body temperature from the mid-period of tilting in SHRs (Figure 5a). Neither spontaneous baroreflex sensitivity nor any of the spectral parameters changed significantly with tilt in diazepam-treated SHRs (data not shown).

Even though diazepam normalized the BP of Wistar rats in the horizontal position (Table 1), orthostatic BP elevation without tachycardia was preserved (Figure 5d).

Effect of chloralose

Chloralose also prevented a rise in BP, HR (Table 1) and body temperature (data not shown) in SHRs during the horizontal body position that preceded the tilt tests except for HR before the head-up tilt test. A sustained but delayed rise in BP due to orthostatic (max: 36.0 ± 7.3 mmHg) and antiorthostatic (max: 42.9 ± 10.9 mmHg) challenges was elicited by chloralose and accompanied by tachycardia (max: 63.7 ± 21.8 BPM and 82.8 ± 25.4 BPM, respectively; Figure 5b). The temperature change in the SHRs induced by sustained tilting was also prevented by chloralose treatment (Figure 4b). Similar to the control measurements, the decrease in spontaneous baroreflex sensitivity was accompanied by a reduction in the LF/HF ratio during the sustained head-up tilt test in chloralose-treated rats (Figure 3a). In the sustained antiorthostatic challenge, only spontaneous baroreflex sensitivity reduction was observed during the head-down tilt test following chloralose administration (Figure 3b). Chloralose treatment also normalized the initial BP and HR values in Wistar rats (Table 1) but sustained the orthostasis-induced BP increase (Figure 5c).

Table 1 Cardiovascular parameters preceding tilt tests

	SHR				
	Repeated				
	Orthostasis		Antiorthostasis		
	BP (mmHg)	HR (BPM)	BP (mmHg)	HR (BPM)	Wistar
CTRL	149.7±4.4	264.8±4.7	138.7±4.4	277.5±5.6	
HOR	179.9±4.4*	375.9±12.1*	181.4±4.8*	375.6±13.6*	

	Sustained						Sustained	
	Horizontal		Orthostasis		Antiorthostasis		Orthostasis	
	BP (mmHg)	HR (BPM)	BP (mmHg)	HR (BPM)	BP (mmHg)	HR (BPM)	BP (mmHg)	HR (BPM)
CTRL	153.4±4.5	270.9±8.8	147.2±5.7	261.7±2.8	151.0±6.4	276.0±5.9	108.9±2.8	336.1±7.6
HOR	177.6±3.7*	371.1±10.4*	180.4±5.2*	364.5±5.0*	183.1±4.2*	378.5±10.1*	116.4±2.8*	390.0±7.7*
CTRL			187.4±6.5	318.9±11.3	167.2±6.3	321.2±10.8	112.4±2.3	342.9±10.4
HOR+Diazepam			184.9±10.3	378.7±22.3	184.1±8.1	391.2±18.7	118.4±2.4	437.0±12.5*
CTRL			145.4±4.8	253.6±7.0	150.1±3.8	261.7±6.6	103.9±2.0	317.9±7.7
HOR+Chloralose			156.7±9.1	334.8±20.4*	143.2±8.2	291.3±12.9	106.0±2.3	364.9±19.0
CTRL+VL			154.5±4.7	248.5±8.0	165.9±7.4	255.1±10.5		
HOR+VL			198.9±5.3*	413.4±15.6*	199.2±7.1*	374.8±18.4*		

Abbreviations: BP, blood pressure; BPM, beats per minute; CTRL, traditional cage; HR, heart rate; HOR, horizontal tilt cage; SHR, spontaneously hypertensive rats; VL, vestibular lesioning.
BP and HR of SHRs and Wistar rats in traditional (CTRL) or in horizontal (HOR) tilt cages prior to repeated tilt or sustained horizontal and tilt experiments. Measurements were performed in (i) intact animals, in rats treated with (ii) 5 mg kg^{-1} bw diazepam p.o. or (iii) 26 (SHRs) or 43 (Wistar rats) mg kg^{-1} bw chloralose i.p., or in rats (iv) following VL.
*$P<0.05$ *vs.* CTRL ($n=5$–11).

Vestibular lesioning

After vestibular lesioning, the BP and HR (Table 1) as well as body temperature (data not shown) remained elevated prior to the tilt tests. Both BP and HR decreased significantly during sustained orthostasis (by 12.5±3.2 mmHg and 59.3±17.3 BPM, respectively; Figure 5c). In contrast, sustained antiorthostatic body position induced a significant (20.5±7.1 mmHg) reduction in BP that was not accompanied by bradycardia (Figure 5c). Only the sustained head-down tilt test elicited a further elevation in body temperature in SHRs that were devoid of vestibular cues (Figure 5c). Neither spontaneous baroreflex sensitivity nor the spectral parameters changed significantly during either of the sustained tilt tests (not shown).

DISCUSSION

This study investigated the cardiovascular responses to repeated and sustained changes in body position[18–20] in SHRs and Wistar rats using telemetric recording devices.[30] One of our major findings was that repeated, brief orthostasis results in a transient elevation in the cardiovascular parameters, whereas that of antiorthostasis caused reversible tachycardia in SHRs.

Sustained postural changes in SHRs were either suppressed by the administration of diazepam or elicited by chloralose treatment, where it resulted in a pressor response with tachycardia, and removal of vestibular inputs resulted in a depressor response. In contrast, diazepam had no effect while chloralose enhanced the pressor responses to sustained orthostasis in Wistar rats.

Initial stress response

Transient rises in BP and HR with sustained elevation were observed as a consequence of transferring the SHRs and Wistar rats from their home cages to the horizontal tilt cages (Table 1), as shown previously in Wistar rats[19,20] and similar to Wistar-Kyoto rats and SHRs.[23,25,27] Such a cardiovascular readjustment was accompanied by a steady rise in body temperature in the SHRs. The elevation in physiological parameters before the tilt tests is a common indicator of stress responses evoked by experimental procedures, such as handling, restraint and immobilization or by psychological influences.[23–27,36–41] The amplitude and/or duration of the cardiovascular stress response depends on the strain of rat,[23–27,39,42] the gender[36] and on the type of stress applied.[23,25,36,38,39] Stress responses can also be proportional to intensity[40,43–45] or duration[43–45] of stimuli, and stressors can act additively or synergistically.[25,36,46] Animals may exhibit habituation[24,25,27,36,38,39] or sensitization[25] upon repeated application of particular stressor(s).

In this study, the amplitude of the initial rises in BP and HR exceeded circadian changes and were approximately two to four times higher in the SHRs compared to those in the Wistar rats in this or earlier studies under the same experimental conditions.[19,20] Hyperreactivity preceding the tilt experiments was also observed when cardiovascular responses to some[23–27] but not all[23] stressors were compared between SHRs and different normotensive rat strains.

Rats were familiarized with the experimental procedures and entered the cages voluntarily without exhibiting any sign of stress, for example, aversive behaviors or visible agitation, as seen in acute[19,20] and chronic[17] tilt studies. Despite the rats being accustomed to handling and transferring from regular to tilt cages, initial cardiovascular stress responses did not exhibit any habituation.

Such elevation in cardiovascular parameters could be crucial for the subsequent tilt responses, because reactivity to stress largely depends on the baseline physiological parameters before application of a specific stimulus, as noted by Hjemdahl *et al.*[40]

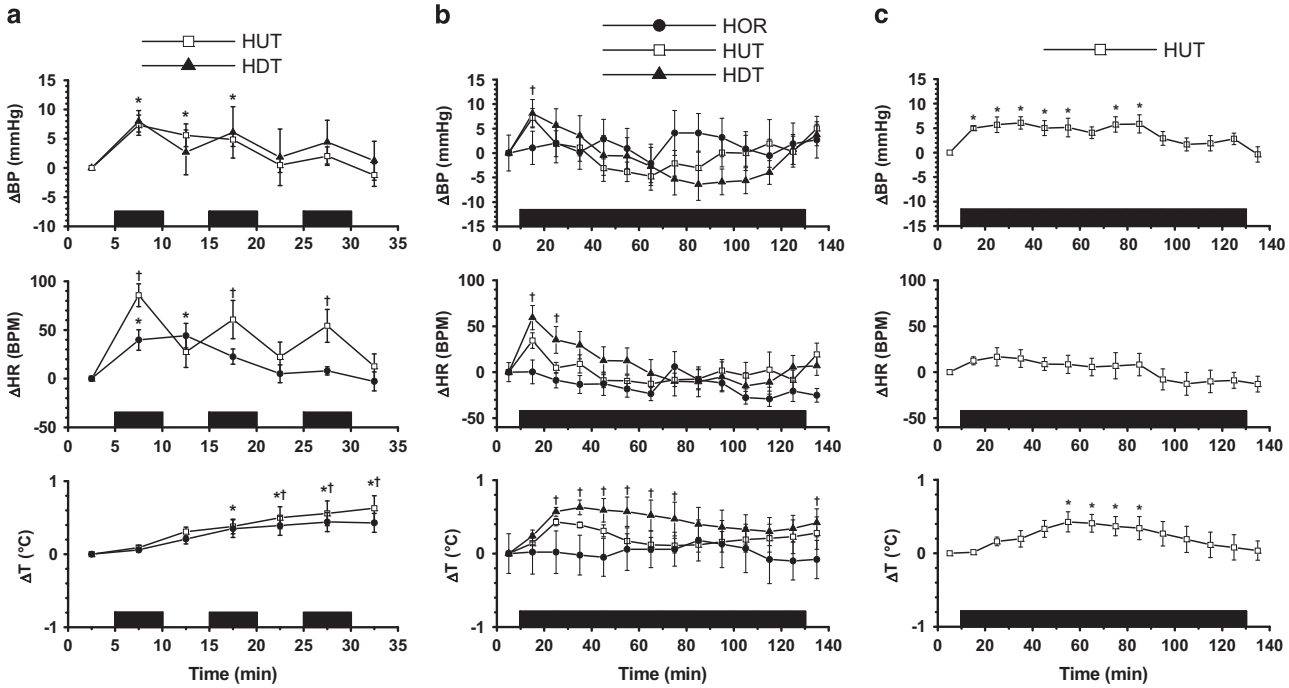

Figure 3 Changes in BP, HR and body temperature (T) relative to horizontal values (Table 1) during (**a**) repeated head-up tilt (HUT) and head-down tilt (HDT), during (**b**) sustained horizontal (HOR), HUT and HDT positions (filled bands) in SHRs, and during (**c**) sustained HUT position (filled bands) in Wistar rats. Statistical differences ($P<0.05$) from horizontal values of HUT and HDT are indicated by * and †, respectively ($n=8$–10).

Temperature elevation observed in the present study implies its specificity to the hypertensive rat strain since either no change or a decrease in body temperature was observed in the normotensive Wistar rats in this and previous studies.[19,20] Similar observations have been made in response to immobilization stress,[26] where SHRs developed more pronounced hyperthermia than Wistar-Kyoto rats.

The anxiolytic diazepam and the sub-anesthetic dose of chloralose were chosen to reduce initial stress responses. As expected, both treatments effectively prevented the initial (augmented) rise in BP, reduced the (amplified) tachycardia and abolished hyperthermia in SHRs and normalized BP and/or HR in Wistar rats preceding the tilt tests. Vestibular lesioning did not affect the initial increase in physiological parameters, indicating that vestibular system does not contribute to the non-specific stress response.

Repeated tilt responses

Repeated exposure to orthostatic body position induced a transient HR elevation paralleled by a rise in BP, suggesting the involvement of both cardiac and peripheral vascular mechanisms. On the other hand, it appears that only the HR-controlling mechanisms were affected during repeated antiorthostasis, because reversible HR changes were not associated with BP elevations. These distinct responses are due to, in whole or in part, the altered cardiovascular responsiveness to brief tilts in different body positions. Finally, the underlying mechanism behind the body temperature rise in response to repeated tilt positioning is probably simple and related to additional gravitational stress regardless of the direction of the tilt. It is concluded that distinct adaptive responses to the short-term changes in body positions are not prevented by the initial augmented rise in cardiovascular parameters.

Sustained tilt responses

Unlike repeated tilt responses in SHRs and sustained orthostatic and antiorthostatic cardiovascular responses in this and previous studies[19,20] in Wistar rats, the SHRs did not exhibit sustained BP and/or HR increases. These data also vary compared to others' observations of tilting-induced BP elevation in SHRs.[42] The exact reason for this difference is obscure but is probably due to distinct experimental procedures, that is, the application of 30 s of passive orthostasis and direct BP measurement by cannulation of the tail artery.[42]

One possible reason for the unresponsiveness to sustained postural changes could be that the cardiovascular hyper-reactivity to environmental stress saturates the cardiovascular reflexes in SHRs that are responsible for longer-term gravitational adaptations.

These assumptions are supported by the following reasons:

1. Unamplified, non-specific stress responses did not prevent pressor or tachycardic responses during sustained tilts in Wistar rats in this or previous studies regardless of resting BP.[19,20]
2. The present study shows no characteristic difference between the responses to sustained head-up tilt and head-down tilt *vs.* the horizontal position in SHRs.
3. None of the sustained body positions caused additional changes in or adaptations to the cardiovascular parameters during the observation period in SHRs.
4. SHRs differentially adapt to sustained and repeated postural changes under environmental stress.

The augmented increase in cardiovascular parameters during the horizontal position was prevented by both diazepam and chloralose. Such a normalization of the baseline parameters by chloralose treatment elicited pressor and tachycardic responses to the sustained tilts in SHRs, whereas these responses were not observed in diazepam-treated SHRs. In contrast, chloralose enhanced while diazepam did not affect orthostatic pressor responses in Wistar rats.

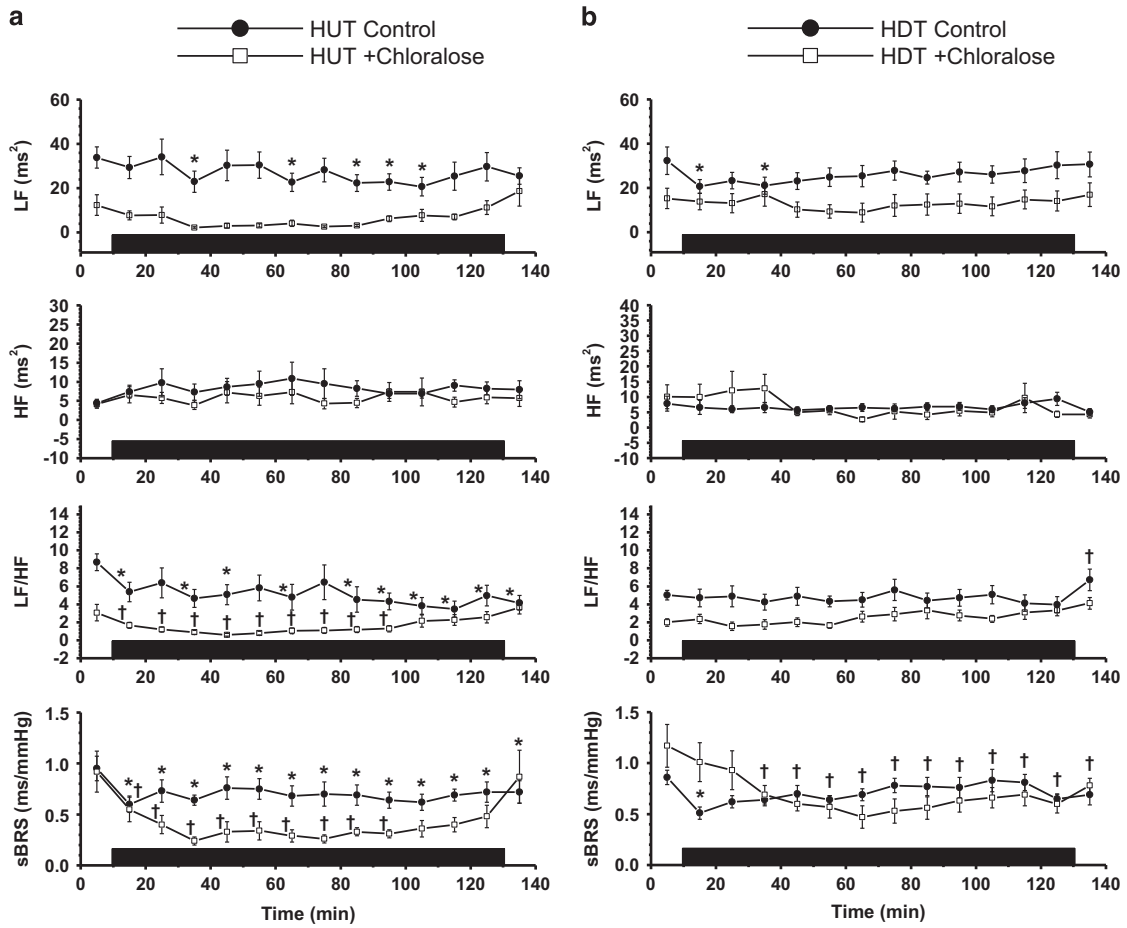

Figure 4 LF and HF components of the power spectrum of HR variability, their ratio (LF/HF) and spontaneous baroreflex sensitivity (sBRS) responses calculated during sustained (**a**) head-up tilt (HUT) and (**b**) head-down tilt (HDT) positions (filled bands) in SHRs. Statistical differences ($P<0.05$) from horizontal values under control conditions and following chloralose treatment are indicated by * and †, respectively ($n=8$).

The amplitude of the cardiovascular changes in SHRs was similar for both the orthostatic and antiorthostatic groups following chloralose treatment and was comparable to the chloralose-induced reduction in baseline cardiovascular parameters. The BP rise with tachycardia in SHRs exceeded the diurnal changes of the cardiovascular parameters and exceeded those found in the Wistar rats in the present and in earlier studies, without substantial changes in HR.[19,20] Consequently, tachycardia was present in the SHRs but absent in the Wistar rats and appears to contribute to the enhanced BP rise during sustained tilt following chloralose treatment, suggesting the participation of both cardiac and vascular effector mechanisms in SHRs.

Diazepam and chloralose had markedly different effects on the tilt responses in SHRs, even though they both effectively reduced the initial stress responses. Both compounds are known to act as positive allosteric modulators of $GABA_A$ receptor channels; however, their activities are exerted via distinct-binding sites of the receptor complex,[47,48] and they might differentially affect specific brain regions that are responsible for cardiovascular stress responses. However, diazepam and chloralose also normalized cardiovascular parameters in the Wistar rats; the former compound preserved while latter enhanced the orthostatic pressor responses.

It is assumed that reflexes responsible for the cardiovascular responses elicited by either non-specific stress or changes in body position (visual information, vestibulo-sympathetic reflex, gravity-related somatic reflex and so on) converge on the same cardiovascular center in the brainstem. Activation of any stress response eventually results in a classic stress reaction via the sympatho-adrenal system, as well as the hypothalamic–pituitary–adrenocortical axis with a characteristic cardiovascular and hormonal response pattern.[40,49–52]

Furthermore, based on changes in plasma stress hormone levels, animal handling also seems to be a more intense stressor than the orthostasis itself.[51]

While non-specific stress responses preceding tilts seem to be a dominant factor under control conditions in SHRs, following its pharmacological elimination, the specific cardiovascular reflexes linked to changes in body position assume dominance. In addition to the anxiolytic effect of diazepam, the compound suppresses BP and HR,[53] which might remain low during tilts and result in unchanged cardiovascular parameters in SHRs but not in Wistar rats. In contrast, chloralose decreases the non-specific environmental stress without depressing cardiovascular reflexes,[54,55] eliciting tilt-induced pressor responses with tachycardia in SHRs and enhanced orthostatic pressor responses in Wistar rats.

The sympatho-adrenal mechanism must play a dominant role in adaptation to postural changes because orthostatic cardiovascular responses are attributed to sympathetic activation.[51,52] This assumption is also confirmed by our earlier observations, which showed that sustained BP responses to tilts were prevented by prazosin in Wistar rats,[19,20] while in other studies, SHRs developed orthostatic hypotension only following prazosin treatment[56] or anesthesia with autonomic

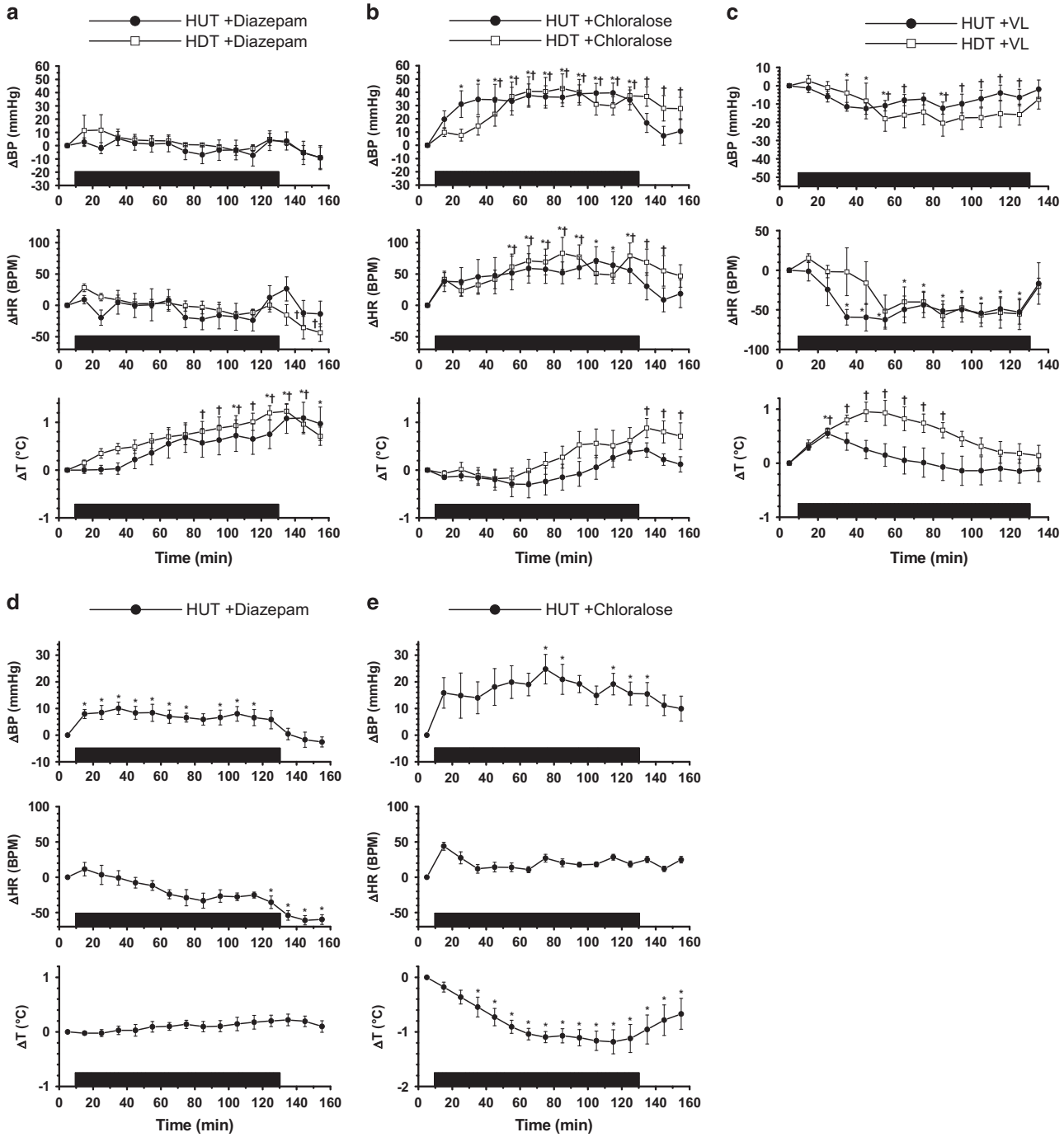

Figure 5 Changes in BP, HR and body temperature (T) relative to horizontal values (Table 1) during sustained head-up tilt (HUT) and head-down tilt (HDT) positions (filled bands) in SHRs treated with (**a**) 5 mg kg^{-1} bw diazepam, treated with (**b**) 26 mg kg^{-1} bw chloralose or (**c**) following vestibular lesioning (VL) and in Wistar rats and treated with (**d**) 5 mg kg^{-1} bw diazepam or (**e**) 43 mg kg^{-1} bw chloralose. Statistical differences ($P<0.05$) from horizontal values of HUT and HDT are indicated by * and †, respectively ($n=5$–11).

blockade.[57] In addition to sympathetic activation in response to orthostasis,[51,52] elevation in plasma ACTH and/or corticosterone levels in the early phase of chronic tilts[17,58] can also contribute to the sustained stress responses in SHRs.

Spontaneous baroreflex sensitivity and spectral parameters

The reduced spontaneous baroreflex sensitivity and altered sympathovagal balance suggest that both are responsible for the maintenance of elevated BP in untreated SHRs and for the BP and HR increase in chloralose-treated SHRs during sustained head-up tilt. Anxiety- and fear-like states causing HR increases were associated with opposite changes in the spectral parameters in male Long-Evans rats.[37] In contrast, only reduced spontaneous baroreflex sensitivity can be linked to the BP rise following chloralose treatment in sustained head-down tilt. The exact mechanism of how postural changes (with or without altering sympathovagal balance) reduce spontaneous baroreflex

sensitivity and cause or contribute to increased BP needs to be determined. As a target for future investigations, establishing a potential cause-and-effect relationship between spontaneous baroreflex sensitivity and sympathovagal balance may help to better understand the orthostatic adaptive mechanism(s) in hypertension.

Role of the vestibular system

In coordination with the arterial baroreflex, sensory inputs from the vestibular system are essential for cardiovascular adaptation to orthostasis in both experimental models[21,28] and humans.[15] Removal of the vestibular inputs by labyrinthectomy did not prevent the initial non-specific stress response, but rats failed to maintain their BP in either the sustained head-up tilt or head-down tilt positions. These results provide further evidence that vestibular inputs that initiate the vestibulo-sympathetic reflex support cardiovascular tolerance during orthostatic and antiorthostatic challenges in hypertension, even under the influence of non-specific environmental stressors. Conversely, the adaptive plasticity of the cardiovascular control observed in the absence of vestibular inputs[59] did not occur in our experimental model.

Perspectives

This study demonstrated that orthostatic tolerance (1) depends on the nature of the stimuli in the 1G environment, (2) is maintained by vestibular inputs under non-specific stress and (3) is differentially modulated by anxiolytic and anesthetic agents in SHRs. Thus, these results suggest that individual susceptibility and habituation as well as recovery from various forms of stress are likely contributors to the development and/or aggravation of acute pressor responses during daily physiological activities. The validity and relevance of our findings and above presumptions need to be confirmed in humans. Finally, these insights may provide guidance in the development of therapeutic strategies for managing orthostatic disorders that are associated with situations such as bedrest, drug treatment, vestibular dysfunction and aging, particularly in hypertensive subjects.[29,60–62]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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