Cardiovascular Regulation During Acute Gravitational Changes with Exhaling on Exertion

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ABSTRACT

During gravitational changes or changes in the direction of action in relation to the body, fluid displacements can be observed. In special cases different breathing maneuvers (e. g., exhaling on exertion; Ex-Ex) are used to counteract acute fluid shifts. Both factors have a significant impact on cardiovascular regulation. Eight healthy male subjects were tested on a tilt seat, long arm human centrifuge, and parabolic flight. The work aims to investigate the effect of exhaling on exertion on the cardiovascular regulation during acute gravitational changes compared to normal breathing. Possible interactions and differences between conditions (Ex-Ex, normal breathing) for the parameters $V'O_2$, V'_E, HR, and SV were analysed over a 40 s period by a three-way ANOVA. Significant ($p \leq 0.05$) effects for all main factors and interactions between condition and time as well as maneuver and time were found for all variables. The exhaling on exertion maneuver had a significant influence on the cardiovascular response during acute gravitational and positional changes. For example, the significant increase of V'O2 at the end of the exhalation on exertion maneuver indicates an increased lung circulation as a result of the maneuver.

Introduction

Fluid shifts play a significant role in cardiovascular regulation. During gravitational changes (microgravity or hypergravity) or changes of the direction of action in relation to the body (relative gravitational vector) like orthostasis during postural changes or acceleration sports (car racing or bobsleighing), fluid displacements can be observed.

Hydrostatic pressure difference are minimized during the transition to microgravity, and a fluid shift towards the thorax occurs. Volume receptors are stimulated and register this new situation as an overload of central blood volume (hypervolemia)[1, 2]. The raised venous return increases the cardiac preload, especially in the

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right ventricle, and therefore a transient difference between the right and left ventricular ejection fraction can be observed. Cumulatively, the stroke volume (SV) and cardiac output (CO) also increase over time [3].The heart rate (HR) and mean arterial blood pressure (MAP) behave highly variable during the transition to microgravity. Most studies show a decrease in HR, which is thought to be a consequence of an increased SV [4–6]. Depending on the measurement site or study design, a decrease in MAP, no change, or an increase in MAP are described [5, 7–9].

Various breathing maneuvers such as the Valsalva maneuver can have the opposite effect. The Valsalva maneuver is a breathing maneuver, characterized by forced exhalation against a closed glottis and/or nose [10, 11]. This maneuver increases intrathoracic and intraabdominal pressure due to resistance. The hemodynamic effects of this pressure increase can be separated into different phases. Due to the increased intrathoracic pressure, there is an increase in SV in the first seconds after the onset of the maneuver, resulting in an initial increase in MAP. A decrease in HR due to stimulation of the baroreceptor. In case, the exhalation pressure is maintained for more than 5 s, the combination of an increased intrathoracic and a decreased intraabdominal pressure cause a virtual collapse of the feeding veins to the right atrium, which reduces venous blood return to the heart. After completion of the maneuver, the sudden venous return and continued elevated total peripheral resistance (TPR) leads to an increased SV and, as a result, a rapid increase in MAP (overshoot) with reflex bradycardia [10–13]. To investigate all different phases, the duration of pressing should be at least 10–15 s. If the period is only 4 to 5 s, usually only the initial hemodynamic effect can be observed [11, 14].

These hemodynamic changes are relevant for the exhaling on exertion maneuver (Ex-Ex) and, therefore, increased tolerance to increased g-forces. In special cases (e. g. transition to hypergravity, increased G-forces in race driving), different breathing maneuvers, for example, a modified Valsalva maneuver or Ex-Ex, are used to counteract acute fluid shifts [14, 15]. During hypergravity, hydrostatic pressure differences are magnified; due to the high G-forces, a fluid shift toward the lower extremities occurs; furthermore, the CO and the MAP decrease due to the lack of venous blood return. The baroreceptors register the pressure and volume differences. The HR is increased, and, it is attempted to increase SV and MAP [4, 16–18]. The exhaling on exertion maneuver encompasses a forced exhalation against the closed glottis and nose for 4–5 s, followed by a rapid exhalation and re-inhalation for a maximum of one second. This maneuver is repeated several times to increase MAP, ensuring adequate venous return through the brief interruption [14–16].

There is only little no research about cardiovascular regulation during acute gravitational changes with Ex-Ex. Schlegel was the first to perform the Valsalva maneuver during a parabolic flight during the microgravity phase [19]. Their experiment showed that there is a decreased stimulation of volume receptors in microgravity. Furthermore, a minimal difference between pulmonary blood circulation and systemic blood circulation is seen in response to acute changes in gravity and body position relative to the force of gravity [3]. There are assumptions that there is a transient difference between right and left ventricular ejection fraction in response to acute gravity differences [3, 20, 21]. The difference between the ejection fractions of the ventricles and the understanding of the effects of physical pressure (e. g., the Ex-Ex maneuver) on the pulmonary vasculature holds potential for diagnosis and further understanding of the pulmonary vascular disease, e. g. idiopathic pulmonary arterial hypertension (PAH). Changes in pulmonary vascular resistance, among other mechanisms, is a pathophysiological explanation of idiopathic pulmonary arterial hypertension [22–24]. Further insights into these mechanisms could provide a valuable contribution to more accurate diagnosis and other therapeutic approaches. To our current knowledge, the extent to which Ex-Ex influences cardiovascular regulation in acute gravitational changes in different conditions and positions has been poorly studied.

The aim of this study is, in addition to the already processed data concerning the resting situation (see [3]), to analyze the influence of Ex-Ex on the cardiovascular regulation after acute gravitational changes in comparison to resting breath situation. Three conditions of gravity changes to the body, tilt-seat, parabolic flight, and long-arm human centrifuge, will be compared. It is hypothesized that Ex-Ex enhances cardiovascular adaptations, i. e. HR, SV, and MAP, during the transition to microgravity or acute positional changes. Like in the study from Hoffmann et al. (2019) this also should imply reactions in $V'O_2$ as an indirect marker for increased lung perfusion.

Materials and Methods

Subjects

The study was reviewed and approved, following the Declaration of Helsinki, by the ethics committees of the Sport University Cologne and for the experiments in parabolic flight by the Center Hospitalier Universitaire de Caen, and by the Agence Nationale de Sécurité du Médicament et des Produits de Santé. Each subject gave written informed consent. The inclusion criteria for the participants were to be male, between 20–40 years old, have good physical health, and a have completed airworthiness examination. Fourteen subjects were included in the study; six had to be excluded due to incomplete data collection in the parabolic and long-arm human centrifuge study conditions. Data from eight subjects (32 ± 3 yr, 182 ± 7 cm, 82 ± 6 kg) were available for all three procedures: the parabolic flight (27^{th}, 28^{th} DLR campaign with the ZERO-G A310 [25]), the tilt seat (Institute of Anatomy and Physiology, German Sport University Cologne), and the long-arm human centrifuge (German Air Force Centre for Aerospace Medicine, Branch I1, Aviation Physiology Diagnostics and Research, Königsbrück).

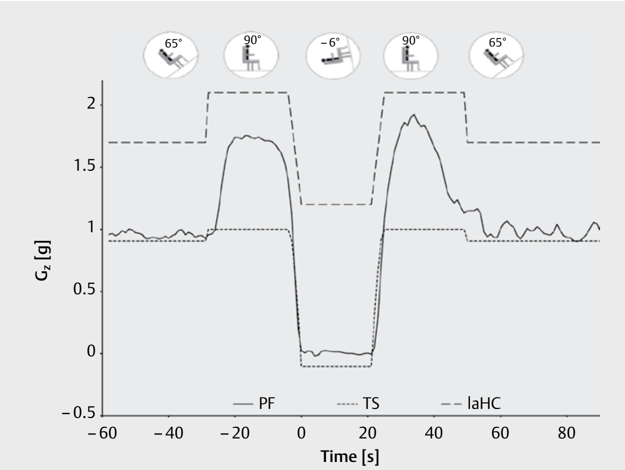
Examination conditions and maneuvers

Subjects were tested in 4 study conditions each (tilt-seat (TS), long-arm human centrifuge (laHC), parabolic flight (PF), control (65 ° sitting at rest)). The acceleration profiles (▶ **Fig. 1**) were aligned in "head to foot direction" (posGz profile).

With a PF maneuver it was possible to create a phase of microgravity lasting about 22 s. During the pull-up, a PF maneuver consisted of increased gravity (1.7 Gz) phases. This hypergravity acted the beginning and end of the parabola and lasted about 22–24 s. The transitions between the phases of hypergravity and microgravity lasted about 3–4 s. The maneuver was initiated at about 6000 m and rose to about 8500 m at the apex of the parabola. Summarized:

each profile has a ≈ 60 s baseline phase (Base), a first ≈ 25 s hypergravity phase (Hyper1), a ≈ 22 s microgravity phase (µg), a second ≈ 25 s hypergravity phase (Hyper2), and a ≈ 50 s recovery phase. The centrifuge offered the possibility to accelerate test persons to increased posGz-forces. The laHC has a 9.5 m rotation axis and can be accelerated to a maximum of + 15 posGz. The laHC had three rotational degrees of freedom that could be controlled independently. For comparison of data from the laHC tp the data from PF, and for feasibility reasons, the acceleration amplitudes were halved. Hence, the baseline level for the laHC was set to 1.7 posGz the hypergravity phases for the PF were simulated with 2.1 posGz, and the microgravity phase by 1.2 posGz. The transition phases between the different posGz accelerations were also based on the posGz profile of PF. The TS is a medical procedure mostly used to diagnose dysautonomia by simulate volume shift. The duration and tilt angle settings were based on the acceleration profile for the PF. The transition phases between the different tilt angles were in accordance with the parabolic flight from the 90 ° position to the –6 ° position four seconds and back to the 90 ° position three seconds. In the TS tests, subjects were tilted manually from 65 ° to 90 °, to –6 °, to 90 °, and back to 65 °. Here, fluid displacements simulated the acceleration and deceleration during the parabolic flights and centrifuge measurements (hereafter referred to as gravitational changes). Using the sinus transformation, the TS angles were fitted to the Gz profiles [26].

A PF contains 31 parabolas in two portions (16/15). The subjects were tested on seven flight days in two flight campaigns. The first subject was tested for each flight day during the first 16 flight maneuvers, and the second during the next 15. All subjects were tested in the study conditions a seated position. During the experiment, subjects completed the following maneuvers in random order with the onset of the microgravity phase: rest, exhaling on exertion, muscle contraction, exhaling on exertion, plus muscle contraction. Each maneuver had been performed a total of four times. Since the second subject completed only 15 flights on the PF, he completed the rest maneuver only three times. This paper presented only the rest and exhaling on exertion maneuvers. Except



▶ **Fig. 1** Acceleration profiles for parabolic flight (PF), centrifuge (laHC), and the tilt angle of the tilt seat (TS).

when performing the exhaling on exertion, muscle contraction, and exhaling on exertion plus muscle contraction maneuvers, the breathing rate was standardized to twelve breaths per minute by an external stimulus. In the exhaling on exertion maneuver, multiple cycles of 4 to 5 s of exhaling on exertion against a resistance (magnetic valve) of 20 mmHg and 1 s of explosive inspiration and expiration were repeated about four times.

The exhaling on exertion maneuver began at maximum inspiration to ensure the same starting position in terms of pulmonary filling. To create a pressure of 20 mmHg, the subject independently blocked the respiratory flow for 3 s using a joystick to a close magnetic valve. In addition, the subject received the verbal commands "Hold – Hold – Out – In" at the appropriate times.

Measuring instruments

In the following, the measuring instruments for the parameters relevant in this work are shown (see ▶ **Table 1**):

- Zan 680 Ergo Test Spiroergometric-System, Zan Messgeräte, Oberthubla, Germany: V'O2, V'CO2, V'E, BF, dFO2et, FCO2et
- Mobil-O-Graph, IEM, Stolberg, Germany: Oscillometric blood pressure according to Riva-Rocci
- Portapres M2, Finapres Medical Systems B.V., Amsterdam, Netherlands: HR, BDsys, BDdia, MAP, SV, TPR

During the examinations, respiratory, cardiovascular, and muscular data, to control muscle contraction during the breathing maneuver, were continuously recorded. The respiratory data, were calculated breath-by-breath and corrected by the algorithm of Beaver et al. [27]. To prevent nasal breathing, the nose was occluded by a nose clip. The measurement principle of the Portapres M2 finger cuff was based on the volume compensation method according to Penaz and Wesseling [28, 29]. Using a height correction unit of the Portapres device, the hydrostatic pressure difference

▶ **Table 1** Overview of measured variables and measuring instruments of the relevant parameters

Parameter	Unit	Measuring instrument/ doftware	Method
Pulmonary oxygen intake ($V'O_2$)	$L \cdot min^{-1}$	Zan 680	Measurement per breath
Pulmonary carbon dioxide delivery ($V'CO_2$)	$L \cdot min^{-1}$	Zan 680	Measurement per breath
Ventilation (V'E)	$L \cdot min^{-1}$	Zan 680	Measurement per breath
End-expiratory oxygen fraction (FO_2et)	%	Zan 680	Measurement per breath
End-expiratory carbon dioxide fraction (FCO_2et).	%	Zan 680	Measurement per breath
Heart rate (HR)	min^{-1}	Portapress M2	Measurement per pulse beat
Mean arterial pressure (MAP)	mmHg	Portapress M2	Measurement per pulse beat
Stroke volume (SV)	mL	Beatscope	Derived from MAP
Cardiac output (CO)	$L \cdot min^{-1}$	Beatscope	Calculated (CO = SVxHR)

between heart level and finger artery was compensated. In addition, there was a correction between finger level and upper arm blood pressures (Mobil-O-Graph).

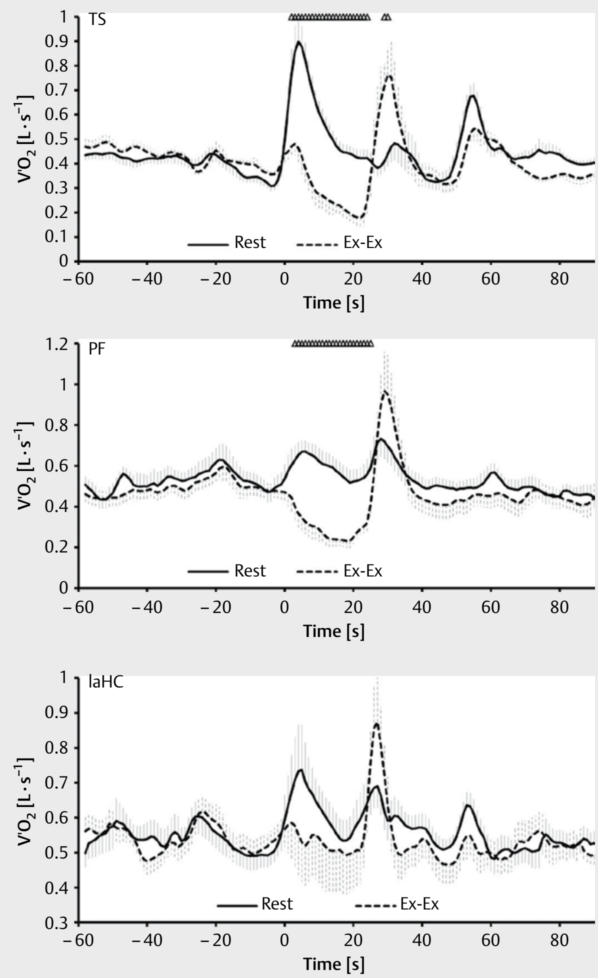
The continuously measured blood pressure was corrected, using linear regression, between the systolic and diastolic upper arm blood pressures values and the systolic and diastolic blood pressures of the Portapres M2 finger cuff. The stroke volume and cardiac output were computed using the Beatscope software (Beatscope 1.1a, Finapres Medical Systems B.V., Amsterdam, The Netherlands), applying the Modelflow Algorithm [30, 31]. Beat-to-beat HR was derived from a 3-channel electrocardiogram. Force sensors recorded a maximum voluntary isometric contraction of the leg extensor, and electromyographic (EMG) data were collected using an EMG amplifier (Biovision) and data storage (Varioport). In order to be able to assess the comparability of the measurements, the ambient temperature, air pressure and relative humidity were noted for all tests.

Data processing and statistical analysis

The breath-by-breath and beat-to-beat were synchronized to ensure a homogeneous recording rate, using trigger signals and interpolated to 1 s intervals. Each measurement sequence started at −58 s (58 s before the beginning of the micro-phase) and ended at 90 s. The data were manually inspected and cleaned for artifacts and outliers caused by, for example, coughing or swallowing.

The graphical representation of the data was done via Microsoft Excel (Excel 365, Microsoft Corporation, Redmond, USA). The arithmetic mean values with standard errors are shown as a function of time. In addition, all values given in the results section are the arithmetic means of the measurement repetitions of the maneuvers with associated standard deviation (mean ± SD).

The statistical analysis was performed with IBM SPSS Statistics (SPSS Statistics 25, IBM Corporate, Armonk, USA). A three-way analysis of variance (ANOVA) with repeated measures (factors: Condition (tilt-seat, parabolic, centrifuge)), maneuver (rest, exhaling on exertion) and time (−10 to 40 s)) was applied. If, the Mauchly test indicated a violation of sphericity ($p \leq 0.01$), the Greenhouse-Geisser correction of degrees of freedom was applied. As post-hoc the Bonferroni test for pairwise comparisons was used. Statistical significance was set to $\alpha = 0.05$. According to Cohen [32], effect sizes were estimated by partial eta squares (η_p^2).

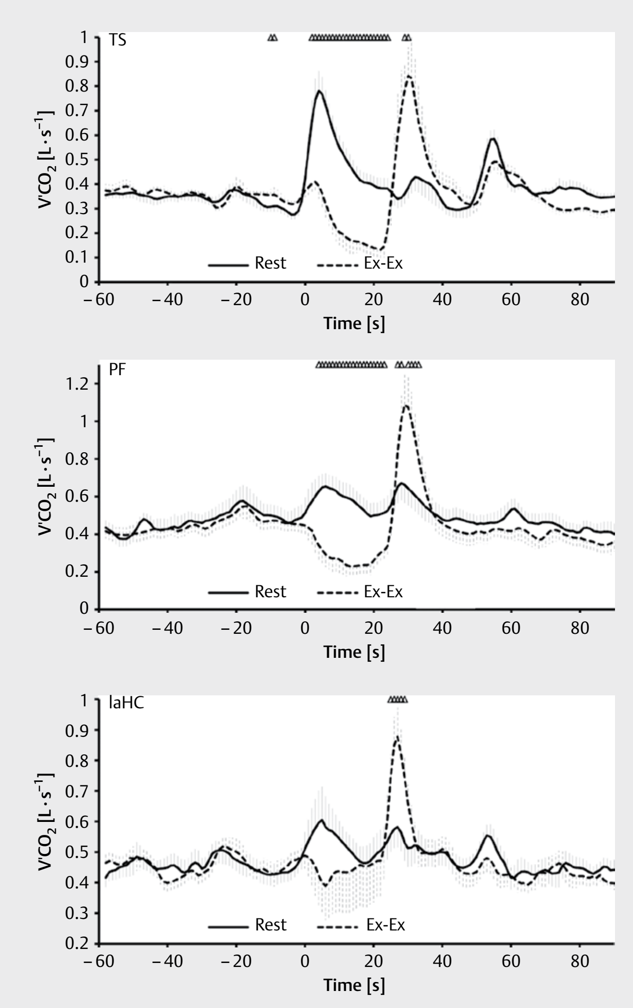


▶ **Fig. 2** Comparison between rest (Rest) and exhaling on exertion (Ex-EX) for $V'O_2$ [L·min⁻¹] for parabolic flight (PF), centrifuge (laHC), and tilt seat (TS). Shown are the arithmetic means with standard error as a function of time. Markers at the top of the diagrams show significant differences between the maneuvers ($p \leq 0.05$).

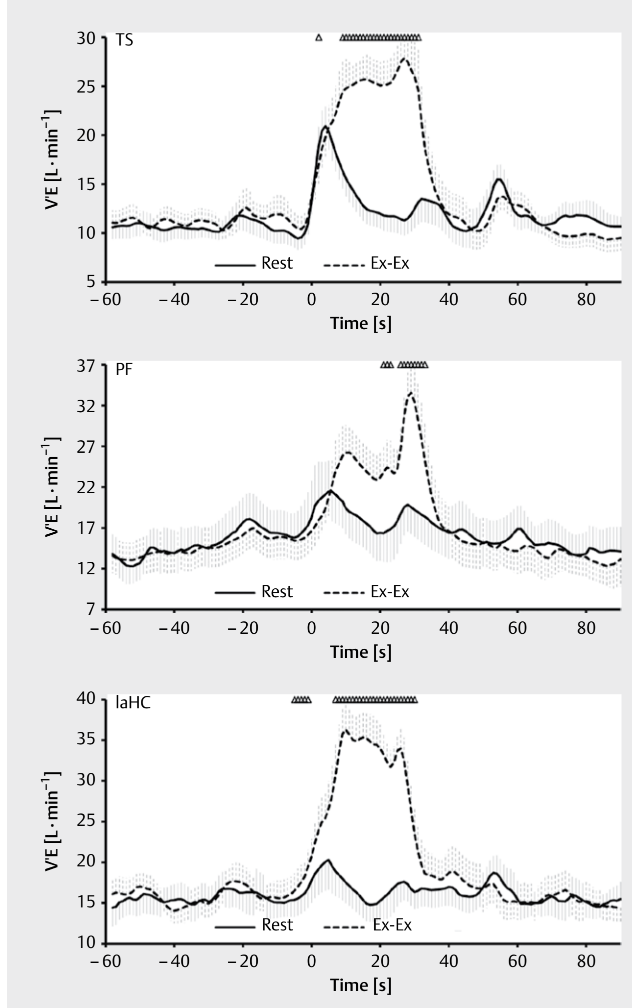
Results

The cardiovascular and pulmonary changes for the resting and Ex-Ex maneuvers during the gravitational changes are presented in ▶ **Fig. 2–8**. Furthermore, the results of each intervention are presented separately (tilt-seat (TS), parabolic flight (PF), and long-arm centrifugation (laHC)). For all parameters, arithmetic means with standard errors of each maneuver for each condition as a function of time, and the significant differences between the ex-ex and resting maneuvers at the respective measurement times in the post hoc tests (corrected according to Bonferroni) are presented graphically (▶ **Fig 2–8**). The results presentation is restricted to a descriptive analysis of the measured and calculated parameters through the periods of experimental conditions and the maneuver. In general, the curves for exhaling on exertion and rest in the resting phases showed an essentially simultaneous course. It was noticeable that the MAP and HR curves are higher for the PF and laHC conditions than for the TS. $V'O_2$ and $V'CO_2$ showed a significant decrease by starting Ex-Ex under all three conditions compared to the resting maneuver (see ▶ **Fig 2** and **3**, 0–20 s). At the end of the Ex-Ex maneuver and with the beginning of the Hyper2 phase there was an increase in $V'O_2$ and $V'CO_2$ in all three condition; the difference was significant for the condition TS and PF (▶ **Fig. 2** and **3**, 25–30 s)). In addition, the Ex-Ex maneuver resulted in a significant increase in ventilation in all three study conditions and again a little peek at the beginning of the Hyper2 phase, most pronounced in the condition PF (▶ **Fig. 4**).

In all three conditions and both maneuvers, the MAP increased with the beginning of the Microgravity. In the PF and laHC, there were hardly any differences between the maneuver and the resting condition. A significant increase in MAP was seen in the TS condition with the onset of the microgravity-phase, while Ex-Ex. A drop



▶ **Fig. 3** Comparison between rest (Rest) and exhaling on exertion (Ex-EX) for V'CO_2 [L·min^{-1}] for parabolic flight (PF), centrifuge (laHC), and tilt seat (TS). Shown are the arithmetic means with standard error as a function of time. Markers at the top of the diagrams show significant differences between the maneuvers ($p \leq 0.05$).

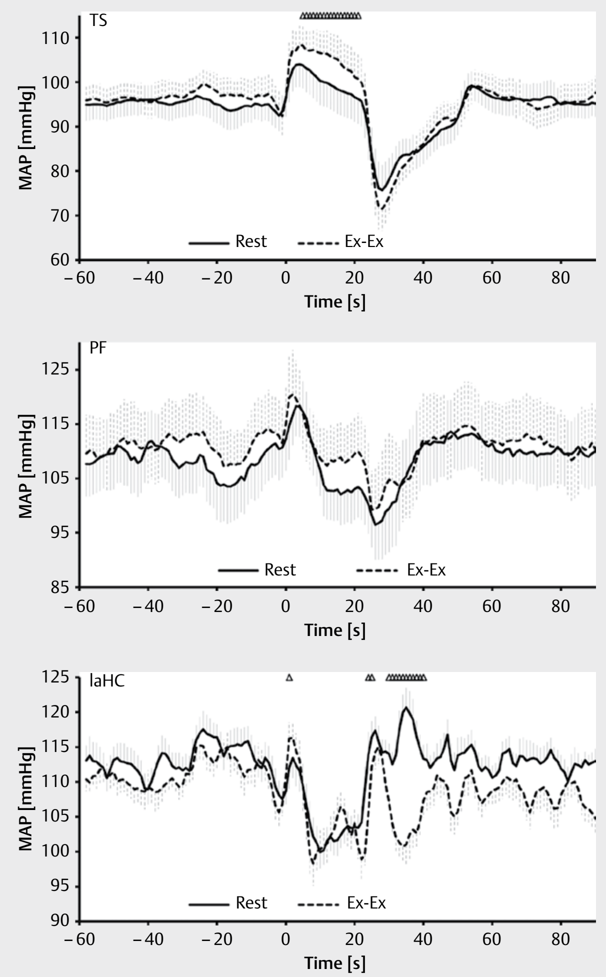


▶ **Fig. 4** Comparison between rest (Rest) and exhaling on exertion (Ex-EX) for V'E [L·min^{-1}] for parabolic flight (PF), centrifuge (laHC), and tilt seat (TS). Shown are the arithmetic means with standard error as a function of time. Markers at the top of the diagrams show significant differences between the maneuvers ($p \leq 0.05$).

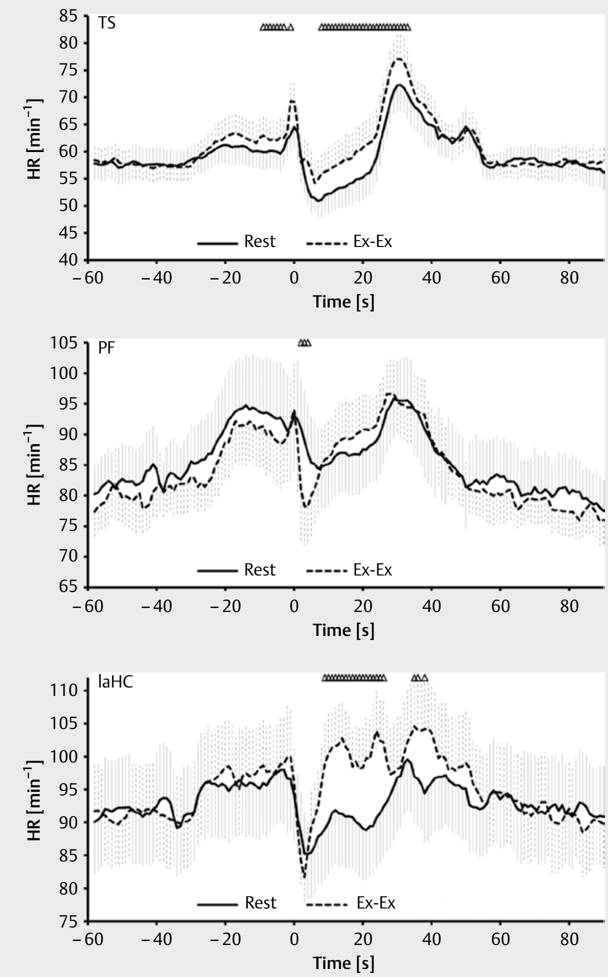
in MAP was perceived in all three examination conditions by the termination of Ex-Ex maneuver at the beginning of the Hyper2 phase. However, this drops significantly below the resting curve in the centrifuge examination (▶ **Fig. 5**). The HR showed an initial increase with the onset of Ex-Ex in all three conditions. A decrease followed the initial increase in HR with a subsequent steady increase. The resting curves also show this progression in PF and TS conditions. In the conditions TS and laHC the Ex-Ex-HR-curve was significant over the resting curve. In the TS experiment, HR during the Ex-Ex maneuver remained steadily above the HR during the resting curve; in the PF measurement, HR was significantly lower than the resting curve at the beginning of the maneuver. HR remains above the resting curve in the laHC and TS even after the end of the Ex-Ex maneuver in the Hyper 2 phase (▶ **Fig. 6**).

In the PF and the TS examination, an initial drop in SV was seen with the onset of the microgravity phase in the resting and ex-ex-conditions. In the ex-ex curves, the SV was always below the resting curve. For the PF, there was no significant difference in the microgravity. In the laHC, both maneuvers (rest and ex-ex) led to an increase in SV at the beginning of the microgravity. While in the resting condition, the SV increases in the microgravity. The SV dropped after the initial increase at the beginning of the ex-ex phase and only levels off again at the end of the Hyper2 phase of the resting curve (▶ **Fig. 7**). No change was seen for CO in the TS experiment. The rest and ex-ex curves run almost simultaneously during all phases. In the PF and laHC conditions, there was a drop in CO during Ex-Ex after an initial increase, which increases significantly shortly, after the end of the maneuver in the Hyper2 phase (▶ **Fig. 8**).

The analysis of variance showed a significant influence of all three main factors $p \leq 0.05$ (time, condition, and maneuver) for the parameters $V'O_2$, V'_E, HR, and SV. Also, the effect size, the partial eta squares (η_p^2) showed a massive effect for these parameters (▶ **Table 2**.) For the parameters V'$CO_2$and CO, a significant influ-



▶ **Fig. 5** Comparison between rest (Rest) and exhaling on exertion (Ex-EX) for MAP [mmHg] for parabolic flight (PF), centrifuge (laHC), and tilt seat (TS). Shown are the arithmetic means with standard error as a function of time. Markers at the top of the diagrams show significant differences between the maneuvers (p ≤ 0.05).



▶ **Fig. 6** Comparison between rest (Rest) and exhaling on exertion (Ex-EX) for HR [min^{-1}] for parabolic flight (PF), centrifuge (laHC), and tilt seat (TS). Shown are the arithmetic means with standard error as a function of time. Markers at the top of the diagrams show significant differences between the maneuvers (p ≤ 0.05).

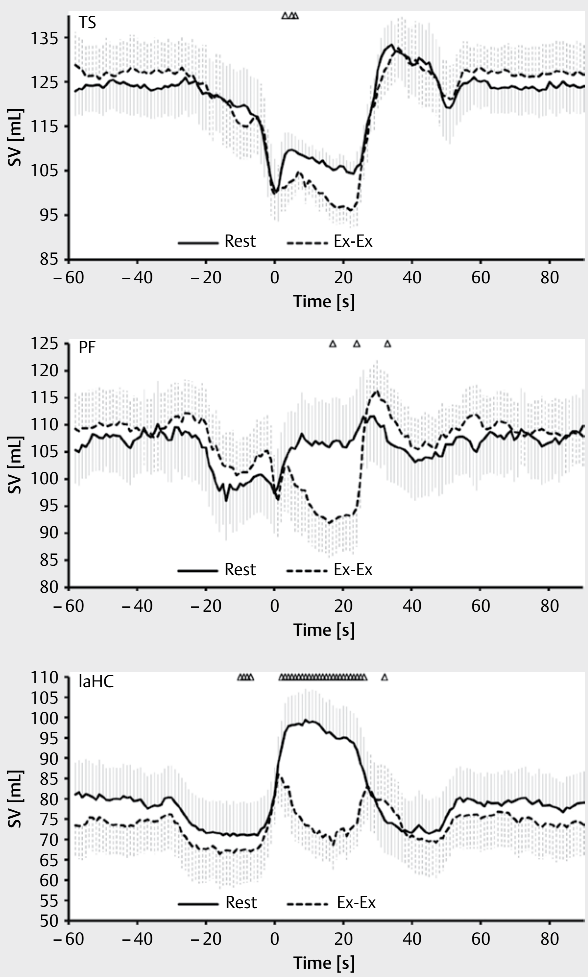
ence and a considerable effect of the main factors time and condition was shown. For MAP, a substantial influence for the factorial time is exhibited (▶ **Table 2**). Furthermore, the three-factor analysis of variance showed a significant interaction between the factors time and condition and the factors time and maneuver for all parameters. For the parameter V'_E, a significant interaction between the factors condition and maneuver was documented. A significant interaction between all three main factors was demonstrated for V'_E, MAP, and SV (▶ **Table 2**), and large effect sizes were observed. For the significant influence of the factor maneuver, the most apparent effect size was calculated for the parameters $V'O_2$ and V'_E followed by the significant interaction between time and maneuver for the parameter SV.

Between conditions a pairwise comparison showed significant differences between TS and laHC for the parameters $V'O_2$ (p = 0.028), V'_E(p = 0.007), MAP (p = 0.018), HR (p = 0.001) and SV (p = 0.001), and between PF and laHC for the parameter SV (p = 0.023) and between TS and PF for HR (p = 0.013) (see ▶ **Table 3**.).

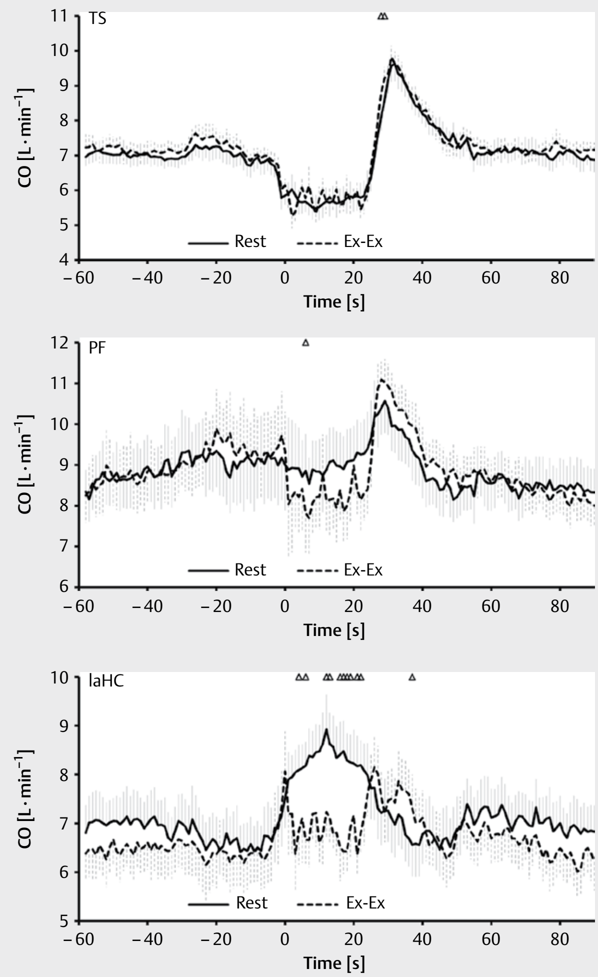
Discussion

This study investigated the influences of Ex-Ex on the cardiovascular system during fluid shifts and gravitational changes in the three study conditions. An effect of Ex-Ex on cardiovascular regulation was observed for almost all parameters. In addition, there were significant differences between the individual study conditions.

Even though the Ex-Ex is a modified Valsalva maneuver, the cardiovascular adaptations can be compared with the classical phases, described by Hamilton [10]. With the onset of the Ex-Ex maneuver, MAP increases in all three study conditions at the beginning of the maneuver. This increase results from the greater intra-abdominal and intra-thoracic pressure with the initially increased return flow to the heart. The high intra-thoracic and intra-abdominal pressure reduce venous return [11, 13, 33]. The HR behaves analogously. After an initial increase, a significant HR decrease occurs due to the activation of the baroreceptor reflex in the PF and TS experiments. The reflex tachycardia can only be observed during the laHC. Analogous to the changes in MAP and HR, due to physiological regulation and



▶ **Fig. 7** Comparison between rest (Rest) and exhaling on exertion (Ex-EX) for the parameter SV [mL] for parabolic flight (PF), centrifuge (laHC), and tilt seat (TS). Shown are the arithmetic means with standard error as a function of time. Markers at the top of the diagrams show significant differences between the maneuvers ($p \leq 0.05$).



▶ **Fig. 8** Comparison between rest (Rest) and exhaling on exertion (Ex-EX) for the parameter CO [L·min^{-1}] for parabolic flight (PF), centrifuge (laHC), and tilt seat (TS). Shown are the arithmetic means with standard error as a function of time. Markers at the top of the diagrams show significant differences between the maneuvers ($p \leq 0.05$).

the omission of venous return, SV and CO are shown to be decreased [11, 13, 17, 33, 34].

With the onset of microgravity, venous return increases causing hypervolemia anterior to the right ventricle. Due to the Frank-Starling mechanism and activation of the baroreceptor and Brainbridge reflex, leads to an increased SV and a reduction in HR [4, 5, 17, 19]. In the PF condition, there are no significant changes in MAP. The resting and Ex-Ex curves are almost identical. A trend towards an increased MAP is visible at the end of Ex-Ex. Schlegel et al. (1998) [19] and Linnarsson et al. (2015) [2] already independently describe a high MAP variability at the onset of microgravity. They represent a decreased sensitivity of cardiac reflexes as the cause of micro-g. The significant increase in MAP during exhaling on exertion in the TS condition supports this assumption.

During PF, the HR shows a significant decrease with the onset of Ex-Ex. It seems that Ex-Ex enhances cardiovascular adaptation in response to microgravity. Because of the hypervolemia due to microgravityand an increased intrathoracic pressure due to Ex-Ex, there is an initial increase in SV and a compensatory decrease in HR. Due to the venous collapse and the reduced SV caused by Ex-Ex, there is slow increase in HR due to less baroreceptor and Brainbridge reflex stimulation. The cardiovascular adaptations allow the excess volume to be removed [5, 10, 35, 36].

The study results show that during the exhaling on exertion, the cardiovascular changes only rudimentarily correspond to the phases of Hamilton. Looga (2005) [11] and Pstras (2016) [13] studies included forced expiration against resistance for approximately 15 s. A modified maneuver is used in our research: the pressure is maintained for only 4 s, followed by an explosive inspiration and expiration. In addition, the breathing maneuver was performed during various gravitational changes in the different conditions (TS, laHC, PF). Schlegel et al. (1998) [19] showed that the classical phases of Hamilton's Valsalva maneuver could not be reproduced entirely in microgravity.

▶ **Table 2** Level of significance of the within-subject factors of the three-way ANOVA (main factors, condition, time, maneuver) and the partial eta squares (η_p^2) for the significant results depending on the parameter. *: $p \leq 0.05$.

	Condition	Time	Maneuver	Condition x Maneuver	Condition x Time	Time x Maneuver	Condition x Time x Maneuver
V'O₂	p = 0.011* η_p^2 = 0.497	p = 0.001*	p = 0.002*	p = 0.292	p = 0,018*	p = 0,017*	p = 0.173
		η_p^2 = 0.558	η_p^2 = 0.770		η_p^2 = 0.352	η_p^2 = 0.474	
V'CO₂	p = 0.042*	p = 0.000*	p = 0.133	p = 0.394	p = 0.013*	p = 0.004*	p = 0.106
	η_p^2 = 0.374	η_p^2 = 0.606			η_p^2 = 0.362	η_p^2 = 0.579	
V'E	p = 0.027*	p = 0.000*	p = 0.001*	p = 0.019*	p = 0.018*	p = 0.001*	p = 0.010*
	η_p^2 = 0.459	η_p^2 = 0.703	η_p^2 = 0.784	η_p^2 = 0.448	η_p^2 = 0.326	η_p^2 = 0.630	η_p^2 = 0.343
MAP	p = 0.060	p = 0.004*	p = 0.668	p = 0.165	p = 0.000*	p = 0.000*	p = 0.031*
		η_p^2 = 0.575			η_p^2 = 0.692	η_p^2 = 0.535	η_p^2 = 0.280
HR	p = 0.001*	p = 0.000*	p = 0.044*	p = 0.114	p = 0.023*	p = 0.022*	p = 0.269
	η_p^2 = 0.769	η_p^2 = 0.652	η_p^2 = 0.460		η_p^2 = 0.356	η_p^2 = 0.373	
SV	p = 0.000*	p = 0.019*	p = 0.013*	p = 0.212	p = 0.000*	p = 0.000*	p = 0.009*
	η_p^2 = 0.754	η_p^2 = 0.445	η_p^2 = 0.612		η_p^2 = 0.668	η_p^2 = 0.773	η_p^2 = 0.365
CO	p = 0.027*	p = 0.000*	p = 0.315	p = 0.458	p = 0.000*	p = 0.000*	p = 0.076
	η_p^2 = 0,442	η_p^2 = 0,742			η_p^2 = 0.665	η_p^2 = 0.511	

▶ **Table 3:** Level of significance of the pairwise comparison of the condition (parabolic flight (PF), centrifuge (laHC), and tilt seat (TS)) over the time (−10s – 40s) depending on the parameter. *: $p \leq 0.05$.

	laHC to TS	TS to PF	PF to laHC
V'O₂	p = 0.028*	p = 0.242	p = 0.252
V'CO₂	p = 0.068	p = 0.161	p > 0.99
V'E	p = 0.007*	p = 0.28	p > 0.99
MAP	p = 0.018*	p = 0.312	p > 0.99
HR	p = 0.001*	p = 0.013*	p = 0.331
SV	p = 0.001*	p = 0.138	p = 0.023*
CO	p > 0.99	p = 0.113	p = 0.072

Another indicator of cardiovascular regulation is pulmonary O_2 uptake. Regarding gas exchange, a significant decrease in O_2 uptake and CO_2 release was observed with the onset of the exhaling on exertion maneuver compared to the resting curve in TS and PF conditions. This decrease results from the prescribed exhaling on the exertion maneuver itself. Due to the pressing and the forced inspiration and expiration, the intrapulmonary pressure and thus also the airway resistance increases, a part of the alveoli collapse, and the pulmonary gas exchange is reduced [13, 37]. With the termination of the Ex-Ex in the Hyper2 phase despite normal breathing, pulmonary O2 uptake increases dramatically. It shows a significant difference in the TS and PF compared to the resting condition. According to the Fick principle, due to the previous venous congestion, massive perfusion of the lung occurs in the subsequent recovery phase. The SV, CO, and HR are also briefly elevated in this Hyper2 phase, confirming the assumption of short-term hypervolemia despite the transition from microgravity to hypergravity.

Another influence on the regulatory mechanisms could be the results shown by Hoffmann et al. (2019), demonstrating a difference between right and left ejection fractions of the heart during the first seconds of the micro-phase during resting maneuver. The increased venous return led to an increased right ventricular SV during micro-phase. In addition, the hydrostatic pressure to the left ventricle was reduced and thus initially led to a reduced filling pressure of the left ventricle. This resulted in short-term congestion of blood in the pulmonary venous system and an ejection difference between the right and left ventricle [3, 21, 38]. Because the pulmonary venous system has increased compliance and operates at lower pressures than the arterial system, it can serve as a blood reservoir [39, 40]. In this study, the stroke volumes for the respective ventricles were not determined as in Hoffmann et al. (2019) [3]. For this reason, the influence of microgravity and pressor breathing on the ejection fraction of the heart cannot be accurately determined. Still, there is evidence that Ex-Ex increases the short-term ejection difference between the right and left ventricles. This is visible in the Micro to Hyper2 transition as described above. The multivariate analyses also showed a significant interaction between condition and time and maneuver and time for all variables. Also the large observed effect sizes suggest that the significant interactions did not occur "by chance" [32]. Even though the absolute Gz differences were the same for all conditions, except for $V'CO_2$, $V'O_2$ and the deliberately induced differences in V'_E, there are significant differences between the study conditions. This is demonstrated graphically and shown to be significant by the statistical analysis. This observation can support the hypothesis that there is a relationship between the volume changes, Gz level and the Gz direction.

This assumption may be relevant to patients with pulmonary vascular disease. The different pathophysiological causes of pulmonary hypertension may lead to diverse ejection differences during simulated microgravity [3]. The regulatory mechanisms and adaptation of SV and HR during this phase may also be relevant for further understanding in PAH. Groepenhoff et al. (2010) [41] hypothesize that patients with PAH have a smaller SV response to exercise compared with left heart failure patients, but a more extensive answer in HR [41]. In their study, Jain et al. (2019) [23] suggest that pulmonary vascular capacity during exercise may be a potential early marker for diagnosing PAH [23].

Limitations

In this experiment, inexperienced subjects (Maneuver and Condition) were tested. Newman (2015) [42] shows that experienced subjects' data are more reliable than inexperienced subjects [42]. This could be one reason why baseline MAP and HR values are lower in the TS test than in the parabola and centrifuge conditions. The possible cognitive influence and the increased sympathetic activity may have a decisive impact on the measured values. Another aspect is the higher posGz level in the laHC experiment as baseline (1.7 g). This led to a slightly increased pressure in the lower extremities and a different baseline value regarding the central blood volume and thus to other stroke volumes [43]. The three conditions can be expected to induce different cardiovascular adaptation responses based on the differences. This complicates the comparison of the test conditions.

For the statistical analysis of the time series analysis, although the condition of normal distribution was not met for some parameters, a three-factor analysis of variance with repeated measures was used. Regression models are generally considered robust to deviation from the normal distribution [44, 45]. For this reason, potentially different p-values could have been obtained. Another limitation was the availability of seats in parabolic flights. The sample was tiny with only eighth subjects, but there was a very good comparability of the samples due to the complete data sets. Even though no power analysis was performed beforehand, the results showed clear influences of the Ex-Ex maneuver on cardiovascular regulation across all conditions.

Conclusion

In conclusion, the exhaling on exertion maneuver influences on the cardiovascular response during acute gravitational and positional changes. The hypothesis that exhaling on exertion enhances cardiovascular adaptation in microgravity and fluid shifts could be confirmed for some parameters: The HR showed in the first seconds a more considerable increase (significant at the condition PF). Also, the MAP was at the conditions PF and TS more stable than when performing the exhaling on exertion maneuver. Even though not explicitly investigated in this study, it could be shown by indirect markers, the significant increase of the $V'O_2$ at the end of the Ex-Ex maneuver, that there are differences between the right and left ejection performance of the heart, as already described by Hoffmann et al. (2019). Further studies are needed to understand the adaption mechanisms because of the physiological complexity of the adaption mechanisms in a wide variety of gravitational changes and fluid shifts. Also, the neuronal and humoral mechanisms that were not analyzed in this study need further attention in the circulatory regulation in gravitational changes and fluid shifts. The presented results can provide relevant hints for a better understanding of PAH and its impacts on physiological regulation and a valuable input for further concepts on new study design.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Notice

This article was changed according to the following Erratum on September 23rd 2022.

Erratum

Andreas Werner and Uwe Hoffmann are sharing the last authorship.