Adaptation of Systemic and Pulmonary Circulation to Acute Changes in Gravity and Body Position

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INTRODUCTION: Changes in gravity or body position provoke changes in hydrostatic pressure in the arterial system and in venous return. Potential asymmetries between left ($\dot{Q}_{LV}$) and right ventricular ($\dot{Q}_{RV}$) cardiac output during transient gravity changes were investigated. It was hypothesized that blood volume is temporarily stored in the pulmonary vessels, with amount and duration depending on the level and directions of gravity.

METHODS: Eight healthy, male subjects (32 ± 3 yr, 182 ± 7 cm, 82 ± 6 kg) were tested on a tilt seat (TS), in a long arm human centrifuge (laHC), and during parabolic flights (PF). The gravitational changes during PF were reconstructed by changing gravity in a laHC and different body positions on a TS. All participants were tested in the seated, resting position. Heart rate and blood pressure were recorded continuously and $\dot{Q}_{LV}$ was calculated, applying the Modelflow Algorithm. Gas exchange was measured breath-by-breath. $\dot{Q}_{RV}$ was calculated from these data according to the Fick Principle. Four sequences were superimposed and analyzed by ANOVA with the factors Time, Ventricle ($\dot{Q}_{RV}$, $\dot{Q}_{LV}$), and Mode (TS, PF, laHC).

RESULTS: After reductions in gravity $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$ were transiently desynchronized. ANOVA showed no main effect for Mode, but significant changes were found for Time and Ventricle and all interactions.

DISCUSSION: Phases of reduced gravity seem to lead to transiently increased storage of blood volume inside the pulmonary vascular system. A more detailed understanding of these mechanisms might help to describe the compliance of the pulmonary vascular system in diseases of the pulmonary circulation.

KEYWORDS: transient gravity changes, pulmonary circulation, systemic circulation.

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Orthostatic or gravitational changes have a significant impact on mean arterial blood pressure (MAP). That is due to changes in hydrostatic pressure with consequences for the arterial pressure, directly, and for stroke volume (SV) and heart rate (HR) caused by an altered venous return to the heart. The resulting pulmonary blood flow is dependent on the dynamic pressure generated by the right ventricle, pulmonary vascular resistance, and the hydrostatic pressure gradients inside the lungs.[2] In a steady state, blood flow in the pulmonary circulatory system (right ventricle to left atrium) must be matched to the flow within the systemic circulation between the left ventricle and right atrium. Short terms of decreased gravity or tilts to the horizontal posture temporarily increase the thoracic blood volume.[9] Therefore, transient differences in flow may occur between the pulmonary circulation and the systemic circulation. In a numerical model, Peterson et al.[11] calculated differences between the volume output of the left and right ventricle with changes in gravity, e.g., during parabolic flight maneuvers. These model data are in line with speculations from tilt table experiments by Toska and Walløe.[20]

Although this has not yet been directly assessed, there are indications for comparable cardiovascular regulations during

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parabolic flights (PF) and tilt table experiments,[15] and similar theoretical considerations during experiments on a human centrifuge.[23] These experiments demonstrate a characteristic, time-dependent asymmetry in cardiovascular responses to inverse variations in gravity forces. In the supine body position, mimicking microgravity, the lung was described as a blood reservoir, leading to an increased left ventricular SV (SV_{LV}) and cardiac output ($\dot{Q}$) after return to a 30° head-up body position.[20]

Assessing asymmetries between the ventricles might be relevant for diagnostics in pulmonary vascular disease, e.g., patients with different types of pulmonary hypertension (PH). Common origins of PH are either a reduced elasticity in the precapillary vascular system (Group 1 of the NICE classification) or elevated left atrial filling pressures as a consequence of chronic left-sided heart disease (Group 2 of the Nice Classification[3]). Referring to these differing etiologies, differences in the responses of SV_{LV} and right ventricular SV (SV_{RV}) would be expected. However, in the experiments of Toska and Walløe,[20] blood flow was measured by ultrasound, targeting the aortic root. Right ventricular output was indirectly estimated from changes in left ventricular output.

There are several methods to estimate $\dot{Q}$; e.g., analysis of the pulse contour wave via finger cuff measurements with application of the Modelflow Algorithm (e.g., Jellema et al.[6] and Wesseling et al.[25]), impedance cardiography (e.g., Kubicek et al.[7]), rebreathing measurements (e.g., Triebwasser et al.[21]), and via the Fick Principle from oxygen uptake ($\dot{V}O_2$) in combination with arterio-venous oxygen concentration differences (a-vO_2 diff) (e.g., Stringer et al.[17]). In view of these methods, the different measurement sites and temporal resolutions should be considered: the first two methods assess the $\dot{Q}$ beat to beat from the left ventricle ($\dot{Q}_{LV}$), whereas measurements based on gas exchange assess the right ventricular output ($\dot{Q}_{RV}$). Applying the Fick Principle, continuous analysis of $\dot{Q}_{RV}$ is possible, as long as a-vO_2 diff remains constant. However, using the rebreathing method, only average values of $\dot{Q}_{RV}$ over a certain amount of breaths can be assessed, but no continuous measurement is possible.

The aims of this investigation were: 1) to describe differences between $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$ after changes in gravity or posture under resting conditions; 2) to investigate the assumptions of Toska and Walløe[20] and the numerical model of Peterson et al.;[11] and 3) to compare the cardiovascular responses to PF, tilting experiments on a tilt seat (TS), and human centrifugation on a long arm human centrifuge (laHC).

The following hypotheses have been developed:

1. $\dot{Q}_{RV}$ is temporarily higher than $\dot{Q}_{LV}$ after decreases in gravity and after tilting from an upright to a supine position.
2. The amount of pulmonary blood volume is influenced by different levels and directions of gravity changes and not comparable to changes in posture.

METHODS

Subjects

The study protocol was approved in advance by the Ethical Committee for Human Experiments of the German Sport University Cologne and the Ethics Committee of the Centre Hospitalier Universitaire de Caen and the Competent Authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé) according to the Declaration of Helsinki (1964, including the amendments until 2013). Each subject provided written informed consent before participating.

Initially, 14 healthy male individuals participated in the experiments. Six subjects had to be excluded from data analysis because of incomplete data acquisition during the PF and laHC. Therefore, the data of eight subjects (32 ± 3 yr, 182 ± 7 cm, 82 ± 6 kg) were available for all three experimental runs during PF (27th and 28th DLR campaign with the Zero-G A310, see Pletser et al.[12] for details), with TS and laHC (Centre of Aerospace Medicine, Aviation Physiology Training Center, German Air Force, Königsbrück, Germany). Before the first test, all subjects were medically certified. In order to study a homogeneous sample, only male subjects were included in the experiment.

Equipment

Throughout all tests, pulmonary oxygen uptake ($\dot{V}O_{2pulm}$), carbon dioxide output ($\dot{V}CO_{2pulm}$), ventilation ($\dot{V}_E$), breathing frequency, and end-tidal fractions of O_2 ($\Delta F_{et}O_2$) and CO_2 ($F_{et}CO_2$) were measured breath-by-breath (Zan 680, Zan Meßgeräte, Oberthubla, Germany). The corrections of Beaver et al.[1] were applied.

HR and blood pressure were measured beat-to-beat with a finger cuff (Portapres M2, Finapres Medical Systems, B.V., Amsterdam, The Netherlands). The hydrostatic difference between the finger and the heart level was corrected using the Portapres height correction unit. $\dot{Q}_{RV}$ was calculated by the Fick principle, according to Stringer et al.[17] $\dot{Q}_{LV}$ and SV_{LV}, as well as total peripheral resistance (TPR), were calculated applying the Modelflow algorithm (Beatscope 1.1a, Finapres Medical Systems, B.V., Amsterdam, The Netherlands). Additionally, blood pressure at the finger level was corrected for upper arm blood pressure (Mobilograph, I.E.M., Stolberg, Germany). Systolic blood pressure was taken from the Finapres data at the moment of maximal inflation of the upper arm blood pressure cuff, diastolic pressure at the moment of complete pressure release from the cuff. Using linear regression between the upper arm systolic and diastolic pressures as well as the Finapres systolic and diastolic pressures, a correction factor was calculated. The continuously measured MAP was corrected with this factor. **Table I** displays the measurement or calculation of relevant key parameters.

Procedure

The acceleration profiles acting in head to feet direction (G_z profiles) for the three different modes (PF, TS, laHC) are detailed in **Table II**. Each profile consisted of a ~60-s baseline phase (Base), a first ~25-s hypergravity phase (Hyper1), a ~22-s microgravity phase (Micro), a second ~25-s hypergravity phase (Hyper2), and a ~50-s recovery phase (Rec). The G_z profile on the laHC was constructed to match the PF G_z protocol but with half of the G_z amplitudes (1.7 G_z, 2.1 G_z, 1.2 G_z, 2.1 G_z, 1.7 G_z). On the TS, the subjects were tilted manually from

Table I. Measurement/Calculation of Key Parameters.

PARAMETER	MEASUREMENT DEVICE	METHOD
Heart rate (HR)	Portapres Device	Beat-to-beat measurement
Mean arterial pressure (MAP)	Portapres Device	Beat-to-beat measurement
Ventilation ($\dot{V}_E$)	Zan 680 Device	Breath-by-breath measurement
Oxygen uptake ($\dot{V}o_2$)	Zan 680 Device	Breath-by-breath measurement
Carbon dioxide output ($\dot{V}co_2$)	Zan 680 Device	Breath-by-breath measurement
End tidal fractions of O_2 ($F_{et}O_2$) and CO_2 ($F_{et}CO_2$)	Zan 680 Device	Breath-by-breath measurement
Stroke volume of the left ventricle (SV_{LV})	Portapres Device	Beat-to-beat measurement
Stroke volume of the right ventricle (SV_{RV})	Calculation	$SV_{RV} = \frac{\dot{Q}_{RV}}{HR}$
Arterio-venous oxygen content difference (a-vO_2 diff)	Calculation	$a\text{-}vO_2\ diff = \frac{\dot{V}o_2}{\dot{Q}_{LV}}$
Arterio-venous oxygen content difference at Baseline (a-vO_2 $diff_{base}$)	Calculation	$a\text{-}vO_2\ diff_{base} = \frac{\dot{V}o_{2base}}{\dot{Q}_{LVbase}}$
Left ventricular cardiac output ($\dot{Q}_{LV}$)	Calculation	$\dot{Q}_{LV} = SV_{LV} \cdot HR$
Right ventricular cardiac output ($\dot{Q}_{RV}$)	Calculation	$\dot{Q}_{RV} = \frac{\dot{V}o_2}{a\text{-}vO_2\ diff_{base}}$
Total peripheral resistance (TPR)	Calculation	$TPR = \frac{MAP}{\dot{Q}_{LV}}$
Accumulated pulmonary blood volume (APBV)	Calculation	$APBV = \sum_{MICRO} (\dot{Q}_{RV} - \dot{Q}_{LV})$

65° to 90° to −6° to 90° and back to 65° (around the horizontal plane) to simulate the accelerations and decelerations (through fluid shifts; in the following mentioned as gravity changes) during PF and laHC. The tilting angles on the TS were calculated to G_z, applying the sinus transformation.[8] Since during the PF the microgravity phase does not start and terminate abruptly, the protocols for the laHC and the TS experiments were adjusted to include transition phases (3–4 s).

A parabolic flight encompasses 31 parabolic flight maneuvers. Overall, seven flights in the two campaigns were available. One subject was tested during the first 16 parabolic maneuvers and one during the following 15 maneuvers. All subjects were tested in a seated position on the TS, PF, and laHC. Within the entire experimental protocol, the subjects performed four different maneuvers in randomized order beginning with the initiation of Micro: rest, exerted exhalation, muscle contraction, or exerted exhalation combined with muscle contraction. In this work, only the rest maneuvers will be presented. Because the second subject of the PF participated in only 15 parabolic maneuvers, he performed only 3 resting maneuvers. None of the subjects took scopolamine before the PF, TS, or laHC experiments.

Table II. G_z Protocol During the PF, the laHC Protocol, and the TS Testing.

	TS[†] (°)	laHC[‡] (G_z)	PF[§] (G_z)
Base[¶]	65	1.7	1
Hyper1[††]	90	2.1	1.8
Micro[‡‡]	-6	1.2	0
Hyper2[§§]	90	2.1	1.8
Rec[¶¶]	65	1.7	1

[†] Tilt seat; [‡]long arm human centrifuge; [§]parabolic flight; [¶]resting phase; [††]first phase of hypergravity, [‡‡](simulated) microgravity phase; [§§]the second phase of hypergravity; [¶¶]recovery phase.

Breath-by-breath and beat-to-beat data of the rest measurements were synchronized using a trigger signal and were then time aligned to 1-s intervals to ensure a homogenous sample rate. The three to four measurements were superimposed and averaged for each second. Outliers, caused by coughing or swallowing, and measuring artifacts were manually eliminated.

$\dot{Q}_{RV}$ was calculated using the measured $\dot{V}o_{2pulm}$ and the a-vO_2 diff calculated via $\dot{Q}_{LV}$ during the last 30 s of each Base. Since no considerable muscular work was performed, a-vO_2 diff [calculated with the averages of $\dot{V}o_{2pulm}$ and $\dot{Q}_{LV}$, according to the Fick Principle, during the last 30 s of Base (a-vO_2 $diff_{base}$)] was assumed to be constant in a limited time frame during the gravity changes. The quotient of $\dot{V}o_{2pulm}$ and the constant a-vO_2 $diff_{base}$ was computed to generate $\dot{Q}$ according to the Fick Principle, finally representing $\dot{Q}_{RV}$. SV_{RV} was calculated as the quotient of $\dot{Q}_{RV}$ and HR. The differences between $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$ were summed up every second, starting with the initiation of Micro, to calculate the accumulated pulmonary blood volume (APBV).

Statistical Analysis

$\dot{Q}_{RV}$, $\dot{Q}_{LV}$, and the respective SVs for 1-s intervals as well as means for the phases were analyzed with a 3-way ANOVA with repeated measures for all factors [Time (−20 s to 20 s), Mode (PF, TS, laHC), Ventricle (RV, LV)]. Post hoc comparisons between $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$ were performed using a Bonferroni test. Statistical significance was set to 0.05 as the alpha level.

RESULTS

The cardiovascular and pulmonary responses during TS, PF, and laHC throughout seated rest during changing gravity or

posture are presented in **Fig. 1**, **Fig. 2**, and **Fig. 3**. The presentation of the results is restricted to a descriptive, albeit comprehensive, analysis of the measured and calculated parameters through the periods of experimental conditions.

In general, subjects showed a higher HR and MAP during PF and laHC compared to TS. In all experiments, there was a steep increase in MAP and a steep decrease in HR in the initial Micro phase. In the transition between Micro and Hyper2, and in the early Hyper2 phase, an increase in HR was observed in all experiments. However, MAP increased only in PF and laHC, while there was a steep MAP decrease in TS (Fig. 1A, Fig. 1B).

Compared to PF and TS, baseline TPR was substantially higher during laHC. Only in the laHC trials, TPR steeply decreased during the transition from Hyper1 to Micro and increased during the transition from Micro to Hyper2, while TS and PF showed an opposite behavior: in these trials, TPR increased between Hyper1 and Micro, while there

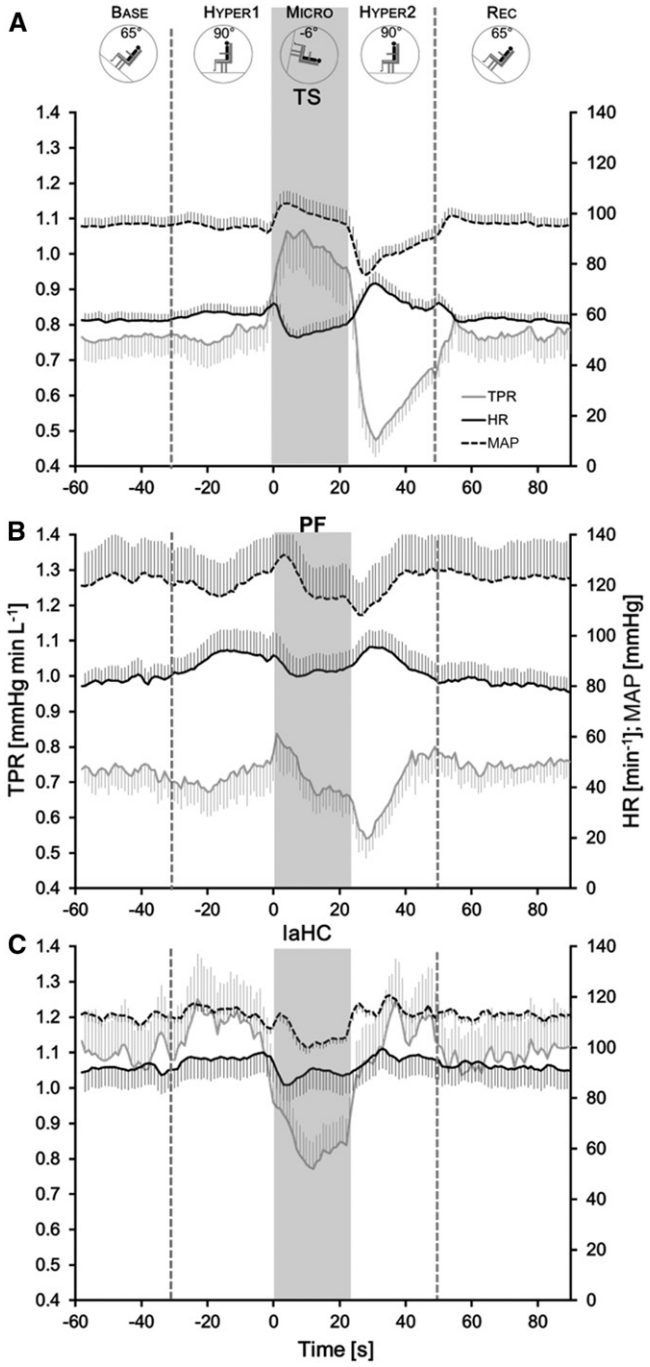

Fig. 1. Cardiovascular responses to changing gravity and body position. HR: heart rate; MAP: mean arterial blood pressure; TPR: total peripheral resistance; TS: tilt seat; PF: parabolic flight; laHC: long arm human centrifuge.

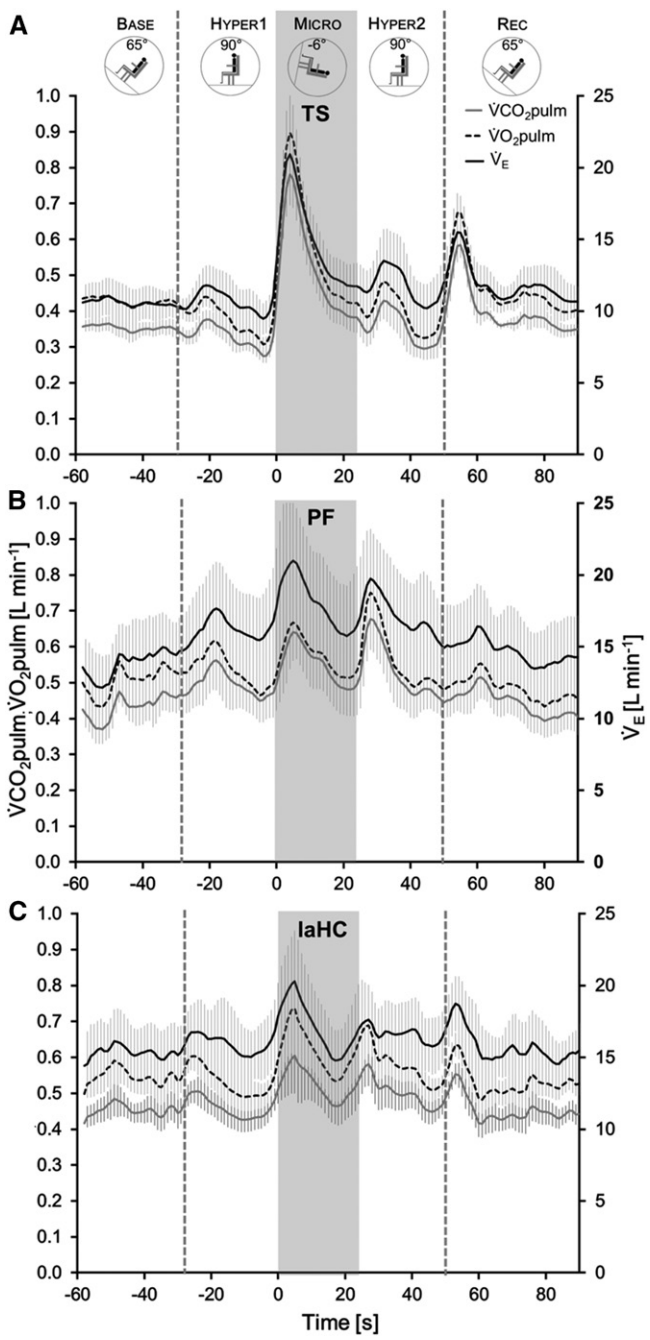

Fig. 2. Pulmonary responses to changing gravity and body position. $\dot{V}O_{2pulm}$: pulmonary oxygen uptake; $\dot{V}CO_{2pulm}$: pulmonary carbon dioxide output; $\dot{V}_E$: ventilation; TS: tilt seat; PF: parabolic flight; laHC: long arm human centrifuge.

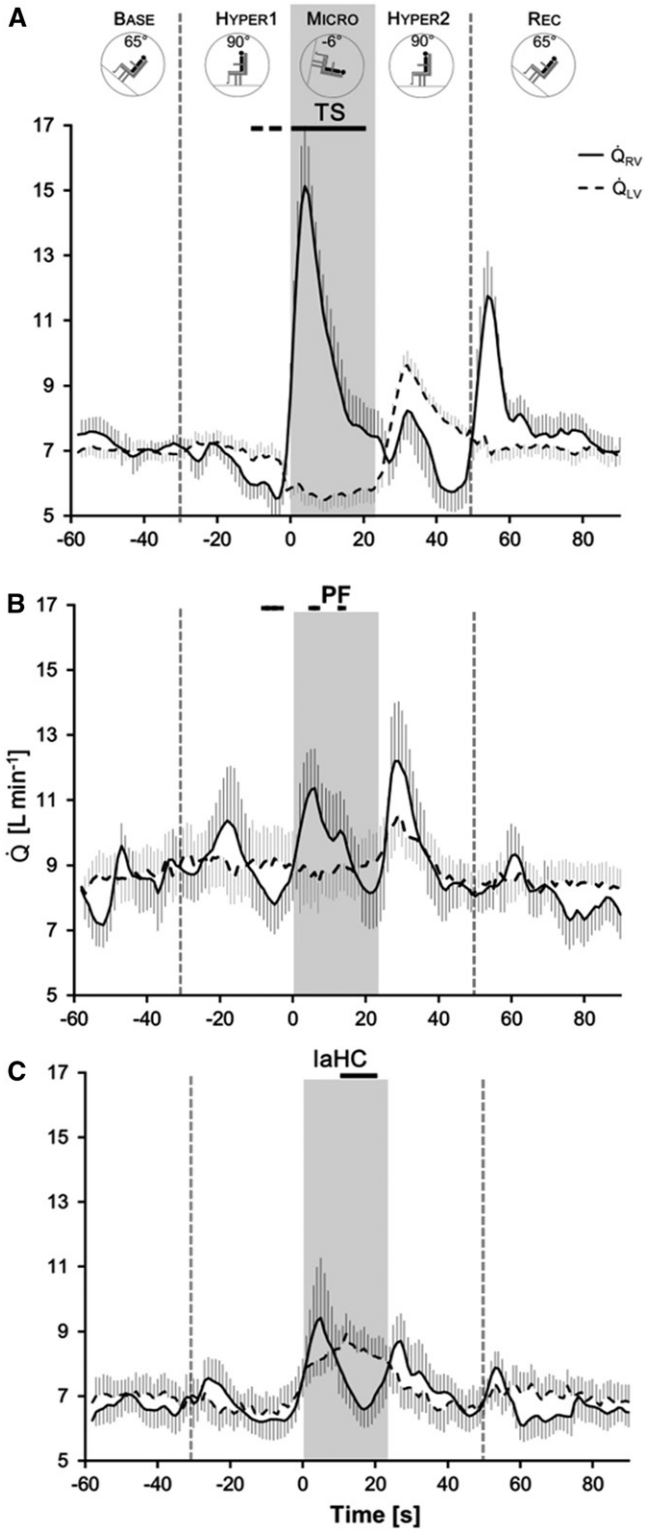

Fig. 3. Responses of the left ($\dot{Q}_{LV}$) and right ventricular cardiac output ($\dot{Q}_{RV}$) to changes in gravity or body position. The black marks (■) above each graph indicate the significant differences ($P < 0.05$) between $\dot{Q}_{LV}$ and $\dot{Q}_{RV}$ (time × ventricle). TS: tilt seat; PF: parabolic flight; laHC: long arm human centrifuge.

was a decrease starting in the late Micro phase, continuing up to early Hyper2. From all experiments, TS showed the highest amplitudes and lowest absolute values for TPR (Fig. 1C).

Gas exchange showed a uniform response in all three experiments (Fig. 2). There was a slight, simultaneous decrease of $\dot{V}_E$, $\dot{V}O_2$, and $\dot{V}CO_2$ during Hyper1, while a sharp increase in $\dot{V}_E$, $\dot{V}O_2$, and $\dot{V}CO_2$ was noticed immediately at the beginning of the Micro phase. The proportion between $\dot{V}_E$, $\dot{V}O_2$, and $\dot{V}CO_2$ changes was similar in all experiments; however, highest absolute changes were seen in Micro during TS (Fig. 2A).

$\Delta F_{et}O_2$ and $F_{et}CO_2$ show a similar behavior during PF and laHC (**Table III**). There was a decrease of $\Delta F_{et}O_2$ and $F_{et}CO_2$ during Hyper1, while an increase was observed during Micro. However, all changes were in the range of less than 1%.

The cardiac output showed substantial differences between TS, PF, and laHC (Mode), as well as between LV and RV (Ventricle) output during the different phases of gravity change (Fig. 3). ANOVA showed no main effect for Mode, but significant effects ($P < 0.05$) were found for Time and Ventricle and all interactions of the factors Time, Mode, and Ventricle. Significances of the post hoc results for $\dot{Q}_{RV}$ vs. $\dot{Q}_{LV}$ are shown in Fig. 3. As a uniform response for all modes, $\dot{Q}_{RV}$ abruptly increased in the transition between Hyper1 and Micro in all trials, with the greatest magnitude during TS in the early Micro phase. In contrast, a corresponding $\dot{Q}_{LV}$ increase in the transition between Hyper1 and Micro was only seen during laHC (Fig. 3C), indicating no significant blood volume shift toward the pulmonary circulation during Micro in this experiment. In PF, $\dot{Q}_{LV}$ did not show any relevant changes during Hyper1 and Micro, whereas $\dot{Q}_{RV}$ was higher in this period (Fig. 3B), resulting a blood volume shift toward the pulmonary circulation. In TS, $\dot{Q}_{LV}$ was even decreasing during Micro. From all three experiments, TS indicated the most pronounced blood volume shifts toward the pulmonary circulation.

$\dot{Q}_{LV}$ and $\dot{Q}_{RV}$ returned to baseline values after Hyper2 in TS, PF, and laHC (Fig. 3). The peak values of the calculated APBV during the Micro phase were highest for TS, intermediate for PF, and lowest for laHC.

For additional information, SV_{RV} and SV_{LV} are summarized in **Table IV**. ANOVA of the 1-s data and the phase averages resulted in significant main as well as interactive effects of the factors. Multiple comparisons of SV_{RV} and SV_{LV} showed similar results for $\dot{Q}_{RV/LV}$ (compare Fig. 3). Obviously, SV_{RV} is generally higher for TS with the highest value in the Micro phase.

DISCUSSION

The combination of pulmonary gas exchange and continuous peripheral blood pressure measurements allows assessing transient differences between $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$, noninvasively and continuously. It was observed, that $\dot{V}O_{2pulm}$ and $\dot{V}_E$ as well as $\dot{V}CO_2$ increase at the same time during Micro (Fig. 2) without similar rises in $\dot{Q}_{LV}$. According to the Fick principle, lung perfusion must be increased during Micro: an isolated elevation of $\dot{V}_E$, which could also increase $\dot{V}O_{2pulm}$, should lead to a reduced $F_{et}CO_2$, which was not observed. An increased a-vO_2 diff causing the increase in $\dot{Q}_{RV}$ without a similar rise in $\dot{Q}_{LV}$ should be neglectable in most conditions. Only during the early Micro

Table III. End Tidal Fractions of Oxygen ($\Delta F_{et}O_2$) and Carbon Dioxide ($F_{et}CO_2$) During the Different Tilting and Gravity Conditions.

	TS[†]				PF[§]				laHC[‡]			
	$\Delta F_{et}O_2$[†††] (%)		$F_{et}CO_2$[‡‡‡] (%)		$\Delta F_{et}O_2$ (%)		$F_{et}CO_2$ (%)		$\Delta F_{et}O_2$ (%)		$F_{et}CO_2$ (%)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Base[¶]	6.92	1.15	5.62	0.87	7.31	1.63	6.01	1.19	6.09	1.06	4.84	0.81
Hyper1[††]	6.17	1.15	5.28	0.86	6.91	1.89	5.98	1.26	5.72	1.20	4.73	0.88
Micro[‡‡]	6.23	1.36	5.40	0.89	6.62	1.88	5.90	1.18	5.87	1.11	4.83	0.75
Hyper2[§§]	5.98	1.10	5.25	0.76	6.83	2.01	5.96	1.28	6.03	1.29	4.96	0.90
Rec[¶¶]	6.60	1.30	5.56	0.94	6.78	1.79	5.92	1.26	5.84	1.10	4.74	0.81

[†] Tilt seat; [‡]long arm human centrifuge; §parabolic flight; [¶]resting phase; [††]first phase of hypergravity, [††](simulated) microgravity phase; [§§]the second phase of hypergravity; [¶¶]recovery phase, [†††]difference of end tidal oxygen fraction; [‡‡‡]end tidal carbon dioxide fraction.

phase during TS is a-vO_2 diff probably elevated during the first seconds, as an excessive amount of venous blood from the legs reaches the pulmonary circulation. Therefore, $\dot{Q}_{RV}$ during the first 20–30 s of the TS Micro phase is most probably overestimated.

Despite this particular caveat, the most impressive differences were found at the beginning of the Micro phase after the highest G_z reduction in all experiments. Therefore, there is strong evidence for diverging time courses of $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$. The hypothesis of a temporarily higher $\dot{Q}_{RV}$ in comparison with $\dot{Q}_{LV}$ after decreases in gravity and after tilting from an upright to a supine position can be confirmed. This divergence might have been caused by the following consequences of G_z reduction and head down tilting, respectively: the hydrostatic pressure in the venous system was reduced during Micro and, for TS, this is indeed a change in G_z direction (see **Fig. 4**). Therefore, in all situations (TS, PF, laHC), venous return to the right ventricle is raised during Micro in comparison with Base and leads to an increased SV_{RV}. At the same time, the hydrostatic pressure toward the left ventricle is reduced in all conditions or even redirected in the −6° position during TS. This initially reduces the filling pressure into the left ventricle. Hence, in the first seconds of Micro, the pulmonary venous system will be filled, resulting in a difference between SV_{RV} and SV_{LV} (Table IV). Since the pulmonary system's vessels are more compliant and the system operates at a much lower pressure compared with the systemic vessels,[13,19] blood can be stored in the pulmonary vasculature,[14] which was earlier described as a blood reservoir.[20]

Similarly, Linnarsson et al.[9] reported increases in thoracic blood volume, assessed by impedance measurements, during the Micro phase in tilt table and PF. In line with this, Toska and Walløe[20] described decreases in $\dot{Q}_{LV}$ measured by Doppler ultrasound during tilt experiments and Peterson et al.[11] calculated differences between left and right ventricular output for PF, applying a mathematical model.

During diving, a redistribution of blood volume of 1.5 L into the lung vascular system with an unknown upper limit is assumed.[10] After a few seconds of Micro, hydrostatic pressure seems to be sufficient to increase SV_{LV}[24] again, according to the Frank-Starling mechanism. During the Hyper2 phase the APBV is pumped out through the left ventricle in the

Table IV. Summary of Resulting Stroke Volumes (SV) for the Right (RV) and Left Ventricles (LV) for the Different Phases and the Different Modes.

	TS[†]		PF[§]		laHC[‡]	
	RV[†††]	LV[§§§]	RV	LV	RV	LV
Base[¶]						
mean	125 ± 20	124 ± 18	104 ± 21	107 ± 20*	77 ± 21	79 ± 22
min	116 ± 34	122 ± 23	88 ± 24	105 ± 17	72 ± 21	72 ± 22
max	133 ± 23	126 ± 21	120 ± 31	110 ± 23	83 ± 26	82 ± 22
Hyper1[††]						
mean	107 ± 24	117 ± 23*	96 ± 21	99 ± 21	70 ± 17	72 ± 22
min	94 ± 35	101 ± 20	85 ± 15	96 ± 20	67 ± 18	71 ± 21
max	140 ± 70	122 ± 22	110 ± 36	102 ± 22	82 ± 21	81 ± 19
Micro[‡‡]						
mean	200 ± 52	107 ± 9*	112 ± 22	106 ± 21	89 ± 25	96 ± 21
min	135 ± 44	101 ± 20	90 ± 23	98 ± 20	74 ± 18	89 ± 19
max	300 ± 89	110 ± 10	138 ± 44	108 ± 21	111 ± 49	99 ± 21
Hyper2[§§]						
mean	108 ± 21	124 ± 13*	108 ± 22	107 ± 21	82 ± 20	78 ± 23
min	93 ± 32	104 ± 8	90 ± 28	103 ± 20	74 ± 19	72 ± 22
max	132 ± 41	133 ± 15	128 ± 40	112 ± 24	95 ± 24	94 ± 21
Rec[¶¶]						
mean	135 ± 28	124 ± 18	101 ± 18	107 ± 20	74 ± 18	78 ± 21
min	92 ± 30	119 ± 23	90 ± 19	103 ± 20	66 ± 18	71 ± 23
max	203 ± 43	130 ± 23	114 ± 27	109 ± 20	89 ± 23	80 ± 21

* Significantly different ($P \leq 0.05$); [†]tilt seat; [‡]long arm human centrifuge; [§]parabolic flight; [¶]resting phase; [††]first phase of hypergravity, [††](simulated) microgravity phase; [§§]the second phase of hypergravity; [¶¶]recovery phase; [†††]right ventricle; [§§§]left ventricle. 'Mean' are mean averages over each phase; 'min' and 'max' are the extreme means in the 1-s traces.

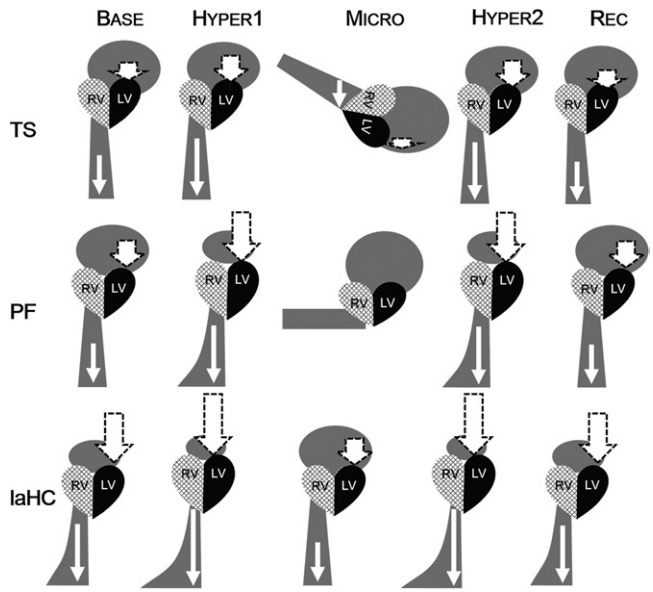

Fig. 4. Influence of gravity on venous volume and hydrostatic pressure. The gray rectangular to triangular shape represents the venous return to the right ventricle (RV). The gray oval describes the venous volume and pressure in the lung, to be transported to the left ventricle (LV). The arrows mark the direction and amount of G_z. TS: tilt seat; PF: parabolic flight; laHC: long arm human centrifuge.

TS and PF condition. The results from Sheriff et al.[16] using tilting experiments are in line with the data found for the left ventricle.

Although the G_z changes for the different conditions were designed with similar amplitudes, only respiratory parameters ($\dot{V}O_{2pulm}$, $\dot{V}CO_{2pulm}$, $\dot{V}_E$) follow similar patterns. These observations confirm the hypothesis of a dependency between the accumulation of blood volume in the pulmonary vascular system and the applied G_z level and direction. One potential reason could be considered the ambient conditions which have a cognitive influence and a modification of sympathetic activity. This can explain the lower HR and MAP in TS since these experiments are performed under well-accustomed laboratory conditions. In contrast, PF, as well as laHC, were relatively novel environments for the measured group of individuals. Another aspect during the laHC condition, with a higher G_z during Base (1.7 g), was the absolute hydrostatic pressure, as discussed above, which explains differences in $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$ caused by an altered inotropic function of the heart.[9,22] The three conditions (PF, laHC, TS) induce different reactions which are not comparable. However, the elevated legs (above heart level) in the TS condition might have amplified venous return from the lower extremities in the cranial direction compared to the recumbent position and/or 0° head-down tilt.[16] Tilt table experiments with straight legs might be more comparable to PF conditions.

The results might also be relevant for clinical application. The APBV was considered to be the blood volume stored in the venous system of the lungs. The amount of APBV might give information about the compliance of the pulmonary vascular system from noninvasive measurements. This effect may be relevant in patients with pulmonary vascular diseases or different types of PH. The different etiologies of PH may lead to characteristic patterns of $\dot{Q}_{RV}$ vs. $\dot{Q}_{LV}$ during changes in body position. PH caused by reduced elasticity of the precapillary pulmonary vascular system might lead to a reduced accumulation of $\dot{Q}_{RV}$ or APBV during TS in the Micro phase. These assumptions have to be verified in future experiments.

Nevertheless, some methodological aspects should be discussed. In this study, SV_{LV} was assessed from the blood pressure signal using the Modelflow algorithm. In the literature, the results of the Modelflow algorithm were compared to other invasive (thermodilution) and noninvasive (Doppler) methods in different set-ups (e.g., Harms et al.[4] and Sugawara et al.[18]). The authors state that at least the relative changes in $\dot{Q}$ provide a reliable estimation with correlation coefficients between the respective methods ranging from $r = 0.78$ to $r = 0.98$. Hence, absolute values must be seen critically. Recently, systematic differences of $\sim 1.5\ L \cdot min^{-1}$ between $\dot{Q}$ measured via rebreathing and $\dot{Q}$ assessed using pulse contour analysis in combination with the Modelflow algorithm during long-duration spaceflight were documented.[5] During the initial Micro phase of PF we observed short-lasting peak differences between $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$ of $\sim 3\ L \cdot min^{-1}$, and during the TS even $\sim 9\ L \cdot min^{-1}$, with these differences lasting only for ~15 s. Therefore, only half of the measured difference during PF can be explained by the results of Hughson et al.[5] disregarding the potential long-term effects of exposure to weightlessness.

Further, a constant a-vO_2 diff can be expected over at least the short time interval of Micro in PF and laHC, since no muscular work was performed during the examined resting period of the experiments. Therefore, $\dot{Q}_{RV}$ and $\dot{Q}_{LV}$ are identical during Base and differences between $\dot{Q}_{RV}$, $\dot{Q}_{LV}$, and the respective SVs can be interpreted.

In the TS experiment though, it is important to note the steep $\dot{Q}_{RV}$ increase in the Micro phase and the resulting unreasonably high SV_{RV}. Even if an increase in SV_{RV} can be assumed, a mean maximum of 300 ml ± 89 ml is out of the physiologically plausible range. The presumption of a constant a-vO_2 diff does not seem to be fulfilled, which is explainable by three potentialities. First, the lower extremities are above heart level and may provoke a pronounced return of venous blood to the right heart, going along with a higher mixed venous a-vO_2 diff due to a higher portion of desaturated blood from the legs. Second, a slightly higher $\Delta F_{et}O_2$ and $F_{et}CO_2$ with an increased ventilation were measured. Third, a higher peripheral resistance was observed (Fig. 1), resulting in a change in the distribution of blood flow from the legs to the right ventricle. Together with the changes in $\dot{Q}_{LV}$, this may cause a change in a-vO_2 diff in the tissues and transiently later at lung level, increasing the error in $\dot{Q}_{RV}$. For Hyper1 and the first part of Micro, this error caused by a-vO_2 diff should be neglectable, but obviously, at latest the data in Hyper2, but also in the last seconds of Micro in the TS, are not reliable and overestimate $\dot{Q}_{RV}$.

The data are useful to quantify noninvasively the relative changes in blood volume stored in the vascular system of the lungs during phases of changing gravity. After reductions of gravity in the TS and PF experiments, an increased amount of

blood is stored in the venous system of the lung. The volume shift is higher during the TS compared with PF experiments. During laHC, no reasonable volume shift was calculated. Therefore, the amount of blood in the pulmonary venous system, due to a mismatch between right and left ventricular output, is influenced by different levels of gravity. Phases of reduced gravity seem to lead to a transiently increased storage of blood volume inside the pulmonary vascular system. The quantification of pulmonary blood volume during reduced gravity or changes in body position might be important to describe the compliance of the pulmonary vascular system and may be evaluated in respective patient groups (e.g., PH and/or chronic left heart failure) in future studies.

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