


RESEARCH PAPER

A comparison between left ventricular ejection time measurement methods during physiological changes induced by simulated microgravity

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Abstract

Systolic time intervals that are easy to detect might be used as parameters reflecting cardiovascular deconditioning. We compared left ventricular ejection time (LVET) measured via ultrasound Doppler on the left ventricular outflow tract with oscillometrically measured LVET, measured at the brachialis. Furthermore, we assessed the progression of the left ventricular ejection time index (LVETI), the pre-ejection period index (PEPI), the Weissler index (PEP/LVET) and the total electro-mechanical systole index (QS2I) during prolonged strict head-down tilt (HDT) bed rest, including 16 male and eight female subjects. Simultaneous oscillometric and echocardiographic LVET measurements showed significant correlation ($r = 0.53$ with $P = 0.0084$ before bed rest and $r = 0.73$ with $P < 0.05$ on the last day of bed rest). The shortening of LVET during HDT bed rest measured with both approaches was highly concordant in their effect direction, with a concordance rate of 0.96. Our results also demonstrated a significant decrease of LVETI ($P < 0.0001$) and QS2I ($P = 0.0992$) and a prolongation of PEPI ($P = 0.0049$) and PEP/LVET ($P = 0.0003$) during HDT bed rest over 60 days. Four days after bed rest, LVETI recovered completely to its baseline value. Owing to the relationship between shortening of LVETI and heart failure progression, the easy-to-use oscillometric method might not only be a useful way to evaluate the cardiovascular system during space flights, but could also be of high value in a clinical setting.

KEYWORDS

head-down tilt bed rest, left ventricular ejection time, oscillometry, systolic time intervals, validation

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1 | INTRODUCTION

Despite improvements in the evaluation of cardiovascular performance and, therefore, more precise individual prediction and follow-up of cardiovascular disease, cardiovascular disease is still the leading cause of death from non-communicable disease (Mendis & World Health Organization, 2014). Classical parameters reflecting cardiovascular performance are cardiac output (CO) or stroke volume (SV) (Bruss & Raja, 2021). The downsides of these measures are the complexity and the lack of easy-to-use non-invasive devices to measure SV and CO accurately (Joosten et al., 2017). Based on newly developed technology and improved signal analysis, systolic time intervals such as the left ventricular ejection time (LVET), pre-ejection period (PEP) and total electromechanical systole (QS2) are receiving new attention. The LVET, PEP and QS2, usually corrected for heart rate (HR) (LVETI, PEPI and QS2I), have been applied since the early 1960s and offer a convenient non-invasive method to study changes in left ventricular performance (Hassan & Turner, 1983). Previous research showed that changes in LVETI and PEPI are well correlated with changes in CO and SV. Moreover, the ratio between PEP and LVET, the so-called Weissler index, was introduced as a measurement to follow individual cardiac responses in patients, especially at home on a daily basis (Lewis et al., 1982; Weissler et al., 1969).

Systolic time intervals can be recorded with several techniques. The advantages and validity of assessing these cardiac function markers using echocardiography or tonometry have been extensively discussed (Aronow et al., 1971; Hametner et al., 2015; McConahay et al., 1972; Paiva et al., 2012; Swaminathan et al., 2003). Echocardiography and tonometry are non-invasive measurement techniques; however, an automatic evaluation without any intervention by health professionals is hardly possible. Our group recently proposed an alternative to these techniques, an oscillometric blood pressure measurement with an inflatable cuff, that is easy to use and automatically evaluable (Bauer et al., 2018).

Major alterations in the cardiovascular system referring to reduced cardiovascular performance are hard to measure because such changes come with age and need years to develop in a normal environment to become clinically relevant. Head-down tilt (HDT) bed rest simulates the effects on humans of microgravity, such as cranial volume shift and physical deconditioning. The model elicits physiological adaptations akin to space travel in a relatively short amount of time (Aubert et al., 2005; Watenpaugh, 2016). Previous studies have shown that prolonged HDT bed rest and real microgravity lower LVET, increase PEP and cause cardiovascular deconditioning (Di Rienzo et al., 2018; Hodges et al., 2010; Iwase et al., 2020; Migeotte et al., 2017). One study presented an increase of LVET and in SV during long-duration spaceflights to the International Space Station (Hughson et al., 2011). Nevertheless, none of the aforementioned studies applied oscillometry allowing for an automatic assessment.

Thus, there were two aims of the present study. First, we aimed to validate easy-to-use oscillometric LVET against the classical echocardiographic LVET, because the study set-up consists of simultaneous measurements using echocardiography and brachial

New Findings

- **What is the central question of this study?**

First, we validated easy-to-use oscillometric left ventricular ejection time (LVET) against echocardiographic LVET. Second, we investigated progression of left ventricular ejection time index (LVETI), pre-ejection period index (PEPI), total electromechanical systole index (QS2I) and PEP/LVET ratio during 60 days of head-down tilt (HDT).

- **What is the main finding and its importance?**

The LVET_{osci} and LVET_{echo} showed good agreement in effect direction. Hence, LVET_{osci} might be useful to evaluate cardiovascular responses during space flight. Moreover, the approach might be useful for individual follow-up of patients with altered ejection times. Furthermore, significant effects of 60 days of HDT were captured by measurements of LVETI, PEPI, QS2I and PEP/LVET ratio.

oscillometry before, during and after intervention. Second, we aimed to investigate the progression of LVETI, PEPI, QS2I and PEP/LVET ratio during 60 days of HDT bed rest, including women and men.

2 | METHODS

2.1 | Ethical approval

In this work, 24 subjects (eight female and 16 male) were enrolled in a joint multidisciplinary HDT bed rest study (AGBRESA, the Artificial Gravity Bed Rest Study) in cooperation between the National Aeronautics and Space Administration (NASA), the European Space Agency (ESA) and the German Aerospace Center (DLR). The study was conducted in line with the *Declaration of Helsinki* and the federal regulations of the US Government. It was registered in the German Clinical Trials Register under number DRKS00015677. The protocol was approved by the ethics commissions of the Medical Association North Rhine (number 2018143) and NASA (Johnson Space Center, Houston, TX, USA). All participants were informed in advance about the aim of the study and signed a written consent form.

2.2 | Study design

All subjects were non-smokers, and none of them had any form of acute heart or arterial disorders that might have affected their systolic time

intervals. Before spending 60 days in strict -6° HDT bed rest, subjects were ambulatory for a 14 day baseline data collection. Subjects were then assigned equally to three different intervention subgroups undergoing either 30 min of continuous artificial gravity per day, six times for 5 min of intermittent artificial gravity per day, or no artificial gravity (control group). Artificial gravity was generated by a short-arm centrifuge in order to reverse the cranial volume shift evoked by HDT. Subjects experienced a radial force of $2g$ on the foot level and $1g$ on the centre of mass. A more detailed description of the countermeasure can be found elsewhere (Kramer et al., 2021).

Oscillometric measurements, obtaining LVET ($LVET_{osci}$) measured at the brachial artery, were taken 6 days before (BDC-6), on the 5th day (HDT05), on the 21st day (HDT21), on the 60th day (HDT60) and 4 days after HDT (R+4). Echocardiographic measurements, obtaining LVET ($LVET_{echo}$), PEP (PEP_{echo}) and QS2 ($QS2_{echo}$) measured with Doppler ultrasound at the left ventricular outflow tract, were taken on BDC-6 and HDT60. Oscillometric and echocardiographic measurements consisted of 10 s continuous recordings. Each 10 s interval of recording was used to obtain a single value of $LVET_{osci}$, $LVET_{echo}$ and PEP_{echo} . The total number of collected measurements analysed was 2,218 for $LVET_{osci}$ measurements (BDC-6 = 508, HDT05 = 427, HDT21 = 383, HDT60 = 521 and R+4 = 379), 220 for $LVET_{echo}$ measurements (BDC-6 = 110 and HDT60 = 110) and 192 for PEP_{echo} measurements (BDC-6 = 96 and HDT60 = 96). Varying measurement numbers in oscillometric measurements come from the different time spans for which the subjects wore the pressure cuff. Moreover, noticeable higher numbers of oscillometric measurements in BDC-6 and HDT60 result from a longer protocol, which included echocardiographic measurements. We included all available data in our analysis. The multiple $LVET_{osci}$, $LVET_{echo}$ and PEP_{echo} and the resulting $QS2_{echo}$ and $PEP_{echo}/LVET_{echo}$ values were averaged to obtain a single value for each subject and measurement time point. Additionally, systolic and diastolic blood pressure (SBP and DBP) were measured using oscillometry.

Subjects were lying in supine position during measurement at BDC-6 and R+4 and in -6° HDT on HDT05, HDT21 and HDT60. Figure 1

illustrates the study design, and the complete measurement set-up is described in our previous work (Möstl et al., 2021; Orter et al., 2020). Methods and algorithms for systolic time interval calculations are described in the following subsections.

2.2.1 | Oscillometric measurements

A method based on numerical derivatives was used to identify the dicrotic notch of a pressure wave. A search window after the systolic maximum pressure was defined. The size of the window was based on the HR but had a minimum size of 220 ms, chosen empirically. Within this search window, the second-order central derivative was calculated to search for the maximum curvature, as follows:

$$\Delta^2 f_i = f_{i+1} - 2f_i + f_{i-1}$$

A detailed description of the algorithm used can be found elsewhere (Bauer et al., 2018). As a result, $LVET_{osci}$ has been defined as the time from the foot of the pressure wave to the incisura of the dicrotic notch. The window-based approach of finding the dicrotic notch is visualized in Figure 2.

2.2.2 | Echocardiographic measurements

The $LVET_{echo}$ and PEP_{echo} in ultrasound were measured based on pulsed Doppler aortic acquisitions at the left ventricular outflow tract. The $LVET_{echo}$ represents the interval from the beginning to the termination of aortic flow, whereas PEP_{echo} was measured as the delay from the beginning of the QRS complex of the ECG wave to the onset of the left ventricular outflow tract Doppler flow. The $QS2_{echo}$ was then calculated as the sum of $LVET_{echo}$ and PEP_{echo} . Additionally, the $PEP_{echo}/LVET_{echo}$ ratio was calculated. Figure 3 illustrates the measurement of $LVET_{echo}$, PEP_{echo} and $QS2_{echo}$ in a representative ultrasound image.

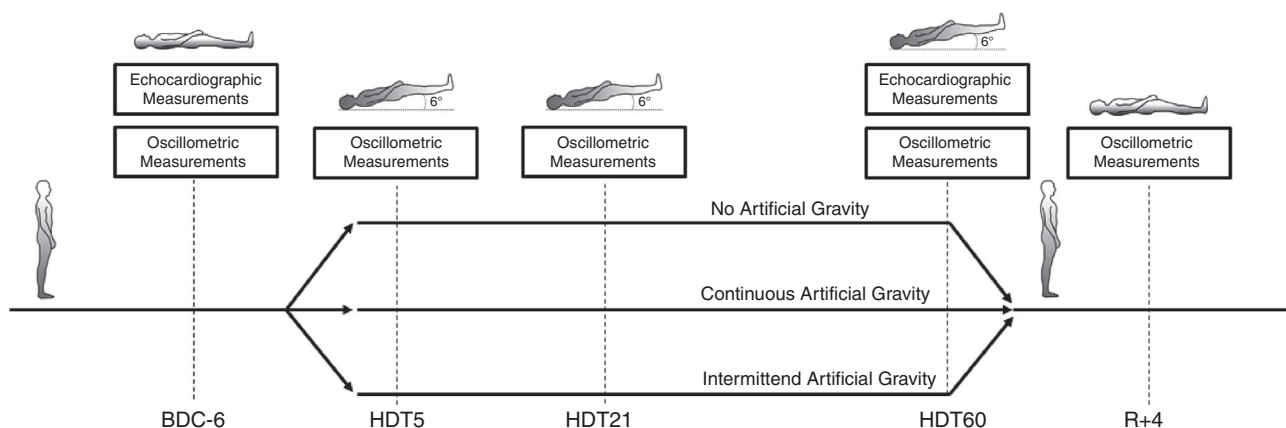


FIGURE 1 Illustration of the study design during 60 days of head-down tilt. Measurements were taken 6 days before (BDC-6), on the 5th day (HDT05), on the 21st day (HDT21), on the 60th day (HDT60) and 4 days after HDT (R+4)

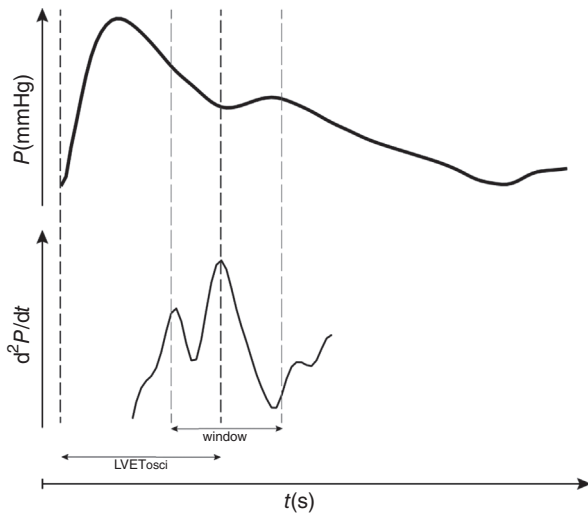


FIGURE 2 Illustration of the dicrotic notch detection in a pulse wave where t describes the time in seconds and P the pressure in mmHg. It shows a pulse wave during one heart cycle and the corresponding second derivative. Search window boundaries, maximum curvature within the search window and beginning of the pulse wave are indicated by vertical dashed lines. Oscillometric left ventricular ejection time ($LVET_{osc_i}$) is defined as the time between the beginning of the pulse wave and the maximum curvature within the search window

TABLE 1 Correction of raw systolic time intervals for heart rate

Sex	Regression equation
Female	$LVETI = LVET + 0.0016 \times HR$
Male	$LVETI = LVET + 0.0017 \times HR$
Female	$PEPI = PEP + 0.0004 \times HR$
Male	$PEPI = PEP + 0.0004 \times HR$
Female	$QS2I = QS2 + 0.0020 \times HR$
Male	$QS2I = QS2 + 0.0021 \times HR$

Abbreviations: HR, heart rate; LVET, left ventricular ejection time; LVETI, left ventricular ejection time index; PEP, pre-ejection period; PEPI, pre-ejection period index; QS2, total electromechanical systole; QS2I, total electromechanical systole index. For all systolic time interval corrections, the same HR was used per subject and measurement time point.

2.2.3 | Heart rate correction

Systolic time intervals are primarily affected by HR. Accordingly, this effect needs to be corrected in order to evaluate cardiac alternations evoked by haemodynamics or contractility. According to the literature, we used different formulas for men and women (Table 1; Lewis et al., 1982).

2.3 | Statistical methods

Multiple measurements per person have been taken at each measurement time point. For statistical analysis, the means for each

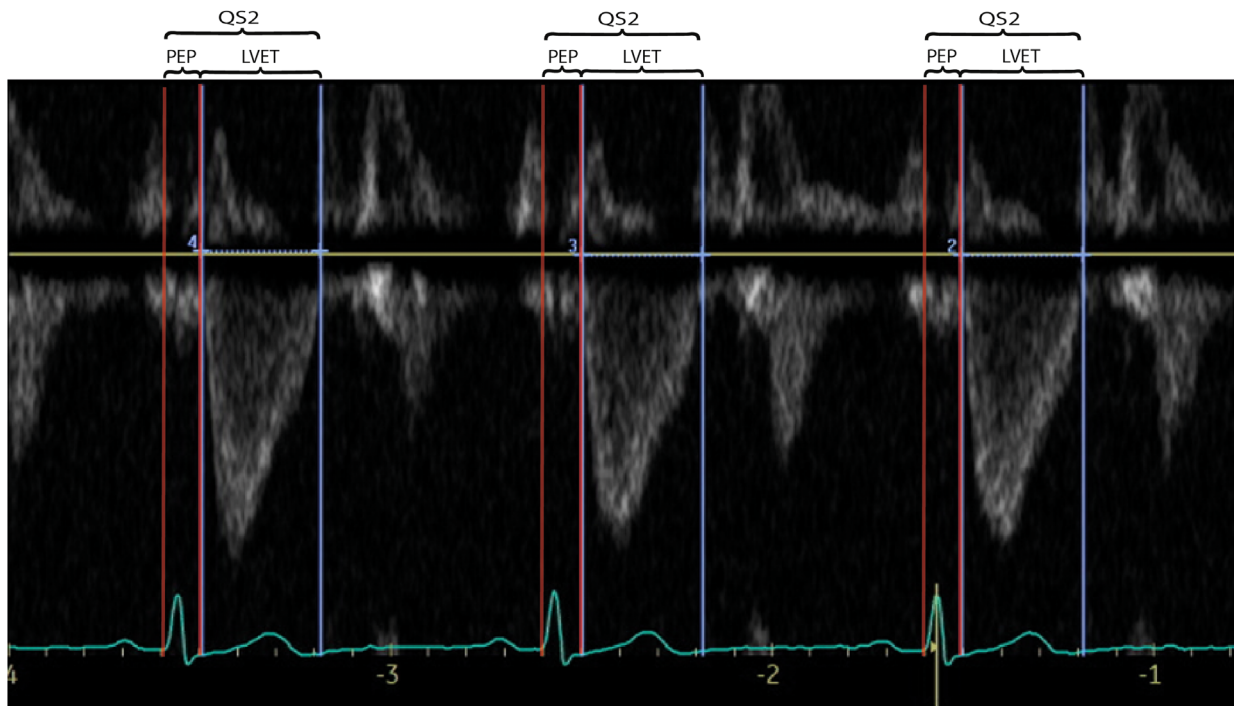


FIGURE 3 Illustration of echocardiographic measurement of echocardiographic left ventricular ejection time ($LVET_{echo}$; blue), echocardiographic pre-ejection period (PEP_{echo} ; red) and echocardiographic total electromechanical systole ($QS2_{echo}$). Grey areas indicate blood flow velocity within the left ventricular outflow tract, assessed by Doppler ultrasound measurements. The cyan line represents the synchronous ECG measurement

subject at specific measurement times were calculated. Continuous data were tested for normality using the Shapiro–Wilk test and explored visually in QQ plots and are presented using mean value and SD.

Method comparison has been done by using scatter plots with linear regression functions and Pearson correlation coefficients, in addition to their *P*-values, Bland–Altman diagrams and four-quadrant plots. The upper right and the lower left quadrants of the four-quadrant plot represent concordant measurements between $\text{LVET}_{\text{osci}}$ and $\text{LVET}_{\text{echo}}$ regarding direction of changes. The concordance rate was then calculated by dividing the number of concordant measurements by the total number of measurements. Analysis was done in SPSS software v.25 (IBM, Armonk, NY, USA) and Matlab R2018b (MathWorks, Natick, Massachusetts, USA).

Linear mixed model (LMM) analysis was performed to assess the effects of repeated measures. The LMM includes the following fixed factors: different measurement time points, the different intervention groups, subjects' age groups and sex, in addition to the interaction terms between measurement time points and intervention groups, measurement time points and sex, age groups and sex, and age group and measurement time points. Age groups are defined according to tertiles: (1) < 28 years; (2) between 28 and 37 years; and (3) > 37 years. Individual subjects were chosen to be random factors to account for repeated measures within participants. The restricted maximum likelihood method was used for fitting the LMM. Post hoc analysis was performed with least significant differences on estimated marginal means and Bonferroni correction. A *P*-value < 0.05 was considered significant, and a *P*-value < 0.001 was considered highly significant.

3 | RESULTS

The mean (SD) height, weight and age of the study population were 174 (9) cm, 75 (9) kg and 34 (9) years, respectively. No significant differences were found between intervention groups, age groups and their interactions in systolic time intervals. Accordingly, the results are represented as pooled data. The mean and SD of each measured parameter at the different measurement time points can be seen in Table 2.

3.1 | Validation of LVET

When comparing oscillometric and echocardiographic measurements of all 24 subjects, linear regression analysis (as shown in Figure 4) revealed Pearson correlation coefficients of $r = 0.53$ ($P = 0.0084$) at BDC-6 and $r = 0.73$ ($P < 0.0001$) at HDT60. The Bland–Altman plots between $\text{LVET}_{\text{echo}}$ and $\text{LVET}_{\text{osci}}$ show an average discrepancy of -0.011 s with limits of agreement of $+0.041$ and -0.062 s at BDC-6 and an average discrepancy of -0.012 s with limits of agreement of $+0.02$ and -0.044 s at HDT60. The cluster of points in the Bland–Altman analyses go from below the mean on the left to above to

the mean on the right, showing a trend proportional to the size of measure.

The four-quadrant plot in Figure 5 shows a high agreement with a concordance rate of 0.96 in directions of the relative effect of $\text{LVET}_{\text{echo}}$ and $\text{LVET}_{\text{osci}}$ between measurement times BDC-6 and HDT60. The mean relative effect over all subjects shows almost perfect agreement between measurement methods.

3.2 | LMM analysis

The $\text{LVETI}_{\text{osci}}$ as measured had a mean value of 0.423 (SD = 0.015) for the baseline measurement 6 days before HDT, a reduction of 4% during HDT and went almost back to normal 4 days after HDT (Table 1). The LMM analysis confirmed these differences in $\text{LVETI}_{\text{osci}}$ ($P < 0.0001$). Post hoc analysis on estimated marginal means showed BDC-6 and R+4 to be significantly higher compared with HDT05 ($P < 0.0001$), HDT21 ($P < 0.0001$) and HDT60 ($P < 0.0001$). Also, $\text{LVETI}_{\text{osci}}$ at R+4 was higher than its baseline value ($P = 0.0250$). The $\text{LVETI}_{\text{echo}}$ showed a decrease of 5% at HDT60 compared with the baseline. The LMM analysis confirmed this reduction ($P = 0.0045$) and showed moderate sex differences ($P = 0.0125$). In contrast to LVETI , we observed a prolongation in $\text{PEPI}_{\text{echo}}$ of 8% after 60 days HDT compared with baseline. Further LMM analysis confirmed this change in $\text{PEPI}_{\text{echo}}$ ($P = 0.0049$). The $\text{QS2I}_{\text{echo}}$ shortening of 2% also showed significance in LMM analysis ($P = 0.0992$) with additional moderate significances between sexes ($P = 0.0223$). The $\text{PEP}_{\text{echo}}/\text{LVET}_{\text{echo}}$ ratio increased between BDC-6 baseline measurement and HDT60 by 20%. The LMM analysis again confirmed the effect ($P = 0.0003$).

4 | DISCUSSION

The objective of this study was to compare standard $\text{LVETI}_{\text{echo}}$ measurements with $\text{LVETI}_{\text{osci}}$ and to analyse changes of systolic time intervals during 60 days of prolonged HDT.

4.1 | Validation of LVET

Our first aim was to investigate an operator-independent method for LVET measurements. The results highlight the potential value of $\text{LVET}_{\text{osci}}$ for examinations without active involvement of health-care professionals. The LMM confirmed differences of $\text{LVET}_{\text{osci}}$ with high significance and $\text{LVET}_{\text{echo}}$ with moderate significance. The $\text{LVET}_{\text{osci}}$ showed smaller SDs compared with $\text{LVET}_{\text{echo}}$ at all measurement time points. The difference between methods might be explained by the fact that the fully automatic procedure of $\text{LVET}_{\text{osci}}$ determination allowed us to perform more measurements, which were available afterwards for calculating mean values per person and time point. Correlation coefficients showed good correlation for BDC-6 ($r = 0.53$, $P = 0.0084$) and HDT60 ($r = 0.73$, $P < 0.0001$), with almost perfectly

TABLE 2 Mean and SD of all measured parameters at all different time points for 24 subjects

Parameter	BDC-6	HDT05	HDT21	HDT60	R+4
HR (beats/min)	62 (9)	58 (10)	65 (11)	69 (12)	72 (10)
SBP (mmHg)	121 (11)	123 (10)	124 (9)	120 (8)	123 (10)
DBP (mmHg)	69 (7)	73 (8)	73 (7)	75 (7)	73 (5)
LVET _{osci} (s)	0.320 (0.015)	0.308 (0.015)	0.301 (0.016)	0.289 (0.017)	0.312 (0.013)
LVET _i _{osci}	0.423 (0.015)	0.405 (0.009)	0.410 (0.013)	0.404 (0.014)	0.432 (0.016)
LVET _{echo} (s)	0.309 (0.031)	–	–	0.277 (0.024)	–
LVET _i _{echo}	0.415 (0.031)	–	–	0.394 (0.024)	–
PEP _{echo} (s)	0.086 (0.010)	–	–	0.094 (0.011)	–
PEP _i _{echo}	0.112 (0.011)	–	–	0.122 (0.011)	–
QS2 _{echo} (s)	0.395 (0.031)	–	–	0.371 (0.027)	–
QS2 _i _{echo}	0.527 (0.031)	–	–	0.517 (0.019)	–
PEP _{echo} /LVET _{echo}	0.282 (0.044)	–	–	0.342 (0.048)	–

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; LVET_{echo}, echocardiographic left ventricular ejection time; LVET_{osci}, oscillometric left ventricular ejection time; LVET_i_{echo}, echocardiographic left ventricular ejection time index; LVET_i_{osci}, oscillometric left ventricular ejection time index; PEP_{echo}, echocardiographic pre-ejection period; QS2_{echo}, echocardiographic total electromechanical systole; QS2_i_{echo}, echocardiographic total electromechanical systole index; SBP, systolic blood pressure. Measurements were taken 6 days before (BDC-6), on the 5th day (HDT05), on the 21st day (HDT21), on the 60th day (HDT60) and 4 days after head-down tilt (R+4).

uniform relationships between LVET_{osci} and LVET_{echo} (regression slope BDC-6 = 1.06 and regression slope HDT60 = 1.01). However, it appeared that high LVET_{osci} values underestimated LVET_i_{echo}, whereas low LVET_i_{osci} values overestimated LVET_i_{echo}. The overall mean difference between oscillometric and echocardiographic measurements was 0.011 s for BDC-6 measurements and 0.012 s for HDT60 measurements. Given that LVET_{osci} was measured at a peripheral site, distant from the heart, this bias could be ascribed to the blood pressure-dependent dynamic changes in arterial distensibility. Higher intravascular blood pressure during systole causes faster wave propagation (Anliker et al., 1968). Therefore, selected fiducial points (beginning of systole and dicrotic notch) wander away from each other as the pulse wave propagates through the arterial tree. Consequently, LVET_{echo} is shorter when measured directly at the aorta compared with LVET_{osci} measured in the periphery, the distal end of origin of the signals (Hegrenaes, 1983). Previous publications reporting comparisons between proximal and distal LVET measurements have shown similar discrepancies to our findings (Chan et al., 2007; Naqvi & Rafique, 2008; Obata et al., 2017).

Changes from baseline to HDT60, visualized in Figure 5, showed high agreement in their effect direction between methods, with a concordance rate of 0.96. The mean effect direction over all subjects also showed an almost perfect agreement, indicating that the intervention can be monitored with both methods alike and reveals the potential for the easily applicable LVET_{osci} measurement during therapy. The approach could be especially appealing when monitoring patients with heart failure. Owing to the relationship between LVET_i shortening and heart failure progression, the ability to detect relative changes in LVET_i at an early stage, be it through worsened myocardial function or volume overload, could be valuable for clinicians (Hametner et al., 2017; Parragh et al., 2015a,b; Patel et al., 2016).

4.2 | Systolic time intervals

Head-down tilt induces changes in the cardiovascular system similar to microgravity in space (Aubert et al., 2005; Watenpaugh, 2016). In our study, these changes were already visible in LVET_{osci} after 5 days of HDT. The LVET_{osci} stayed at a certain level during HDT and increased again thereafter. Migeotte et al. (2017) and Di Rienzo et al. (2018) reported similar decreases of LVET after several weeks of HDT, whereas Hughson et al. (2011) reported rising LVET_i and increasing HR during long-term space flights. Differences in body positions during measurement might explain these discrepancies. In our study, pulse waves were measured in the supine position and -6° HDT, whereas Hughson et al. (2011) published results measured in a seated position but pointed out that LVET_i measurements in the supine position were significantly longer for pre- and post-flight measurements.

When we examined HR and HR-uncorrected LVET_{osci} separately, HR and LVET_{osci} were decreased at HDT05. Aubert et al. (2005) separated the cardiovascular response to HDT into two phases: an initial phase with transient small increases of plasma volume and a secondary phase of hypovolaemia. After 21 days of HDT, subjects were well into the second cardiovascular respond phase. The LVET_{osci} decreased further, but HR increased, maintaining CO in the face of decreasing SV (Hoffmann et al., 2021). These substantial changes in LVET_{osci} during HDT were attenuated 4 days after HDT.

The PEP_i_{echo} had increased on the 60th day, which is consistent with previous studies evaluating PEP during HDT with exercise (Hodges et al., 2010) or lower-body negative pressure countermeasures (Sun et al., 2002). Given that we do not expect the electrical transmission patterns within the heart to change during HDT, increases in PEP_i_{echo} presumably reflect the observed decrease in SV (Hoffmann et al.,

FIGURE 4 Linear regression including Pearson correlation coefficient (r) and regression function (y) in addition to a Bland–Altman plot for 24 subjects. The mean and SD of differences for echocardiographic left ventricular ejection time ($LVET_{echo}$) and oscillometric left ventricular ejection time ($LVET_{osci}$) before (BDC-6) and on the last day of 60 days of head-down tilt bed rest (HDT60) are stated in the Bland–Altman plot

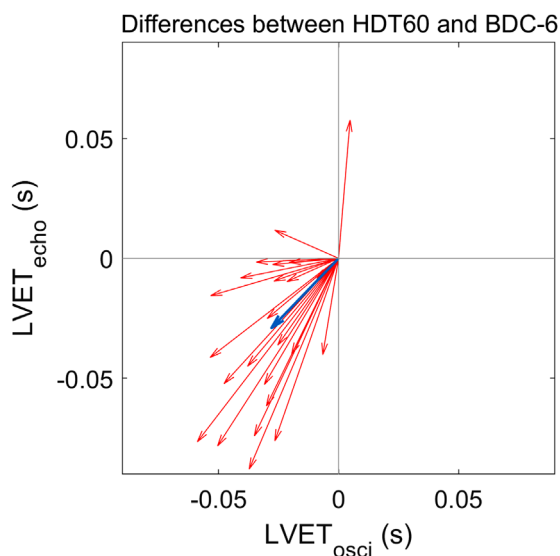
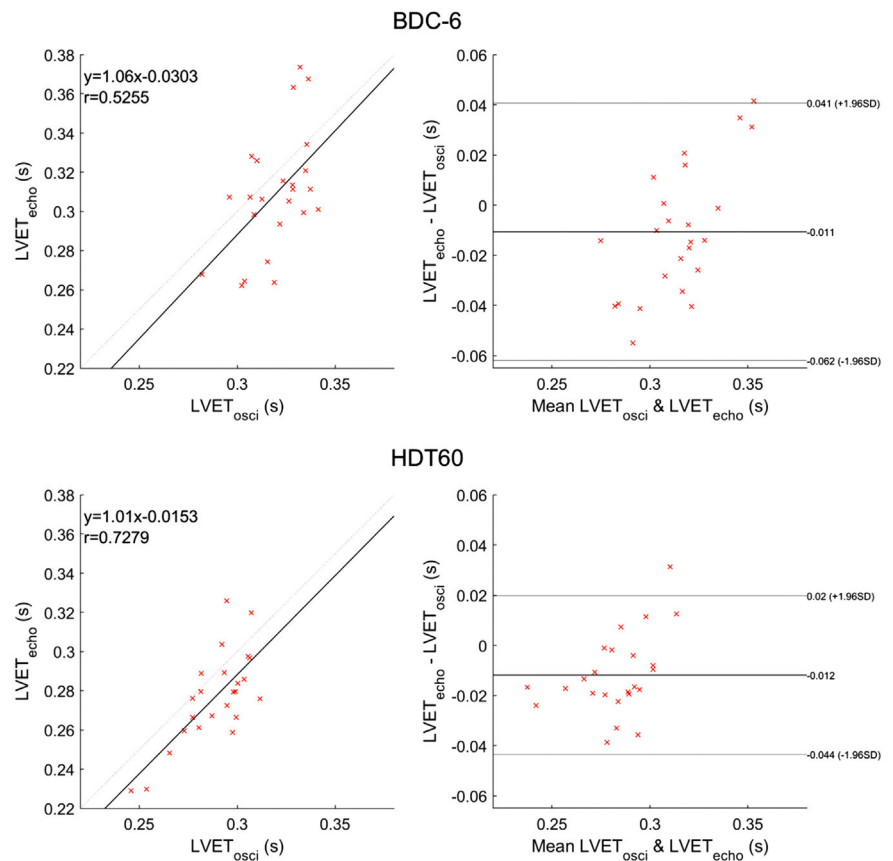


FIGURE 5 Four-quadrant plot of differences between measurement times before (BDC-6) and on the last day of 60 days of head-down tilt bed rest (HDT60) of echocardiographic and oscillometric left ventricular ejection times ($LVET_{echo}$ and $LVET_{osci}$). The upper right and the lower left quadrants of the four-quadrant plot represent concordant measurements between $LVET_{osci}$ and $LVET_{echo}$ regarding the direction of changes. Red arrows indicate effect directions per subject, and the bold blue arrow indicates the mean effect direction over all subjects

2021). An increase in cardiac afterload, as indicated by the increased DBP, would also explain the behaviour of $PEPI_{echo}$ and might even have contributed to the reduction in SV (Boudoulas et al., 1982). Consequently, as $PEPI_{echo}$, $LVET_{echo}$ and $LVET_{osci}$ respond to HDT, their ratio also increases (Di Rienzo et al., 2018; Sun et al., 2001). Given the close relationship between the $PEP/LVET$ ratio and cardiac performance, one might explain this increase as lower performance toward the end of bed rest. However, the methodology cannot distinguish whether these changes are mediated through altered myocardial function or through decreased cardiac preload attributable to blood and plasma volume loss (Lewis et al., 1977). The $QS2_{echo}$ response, which resembles changes elicited through positive inotropic agents, is difficult to explain (Lewis et al., 1977). Possibly, the HR correction formula for QS2 is not applicable when studying long-term cardiovascular adaptation.

None of our findings was influenced by centrifugation as a countermeasure, which reflects the findings in previous published works (Kramer et al., 2020; Möstl et al., 2021).

The generalizability of these results is subject to certain limitations. For instance, the small sample of participants and their wide range of age and varying sex reduces the power of our statistical analysis. Furthermore, our validation in the extreme situation of 60 days of HDT and the presence of fluid shifts and both physiological and psychological stress might also reduce generalizability.

4.3 | Conclusion

The LVET_{osci} and LVET_{echo} showed good agreement in effect direction, and LVET_{osci} even showed lower SDs for each time point. Thus, LVET_{osci} might be a useful additional measure to evaluate cardiovascular responses during space flight in women and in men. Moreover, the approach might be of use for individual follow-up of patients suffering from cardiovascular diseases with altered ventricular timings. Additionally, the effects of 60 days of strict bed rest on the cardiovascular system were captured by measurements of LVETI, PEPI, QS2I and PEP/LVET ratio. Centrifugation as a countermeasure did not influence systolic time intervals, and sex differences were only moderately visible in echocardiographic measurements.

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COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

Experiments were carried out at the Envihab research facility in Cologne, Germany. Data analysis took place at the AIT Austrian Institute of Technology in Vienna, Austria. Data curation: S.O., S.M., M.B. and F.H. Formal analysis: S.O., C.C.M. and B.H. Investigation: S.O., S.M., F.H., C.C.M., E.K., J.T., J.J. and B.H. Methodology: S.O., S.M., F.H., C.C.M. and B.H. Software: S.O. and M.B. Validation: S.O. and C.C.M. Visualization: S.O., S.M. and F.H. Writing – original draft: S.O. and B.H. Writing – review and editing: S.O., S.M., M.B., C.C.M., E.K., M.R., J.T., J.J. and B.H. Conceptualization: M.B., M.R., S.W., J.T., J.J. and B.H. Funding acquisition, project administration and resources: S.W. and B.H. Supervision: B.H. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

DATA AVAILABILITY STATEMENT

Raw data were generated at DLR – German Aerospace Center. Derived data supporting the findings of this study are available from the corresponding author on request.

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