Effects of pericardial constraint and ventricular interaction on left ventricular hemodynamics in the unloaded heart

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Submitted 1 December 2010; accepted in final form 4 March 2011

Fujimoto N, Shibata S, Hastings JL, Carrick-Ranson G, Bhella PS, Palmer D, Fu Q, Levine BD. Effects of pericardial constraint and ventricular interaction on left ventricular hemodynamics in the unloaded heart. Am J Physiol Heart Circ Physiol 300: H1688–H1695, 2011. First published March 11, 2010; doi:10.1152/ajpheart.01198.2010.—Pericardial constraint and ventricular interaction influence left ventricular (LV) performance when preload is high. However, it is unclear if these constraining forces modulate LV filling when the heart is unloaded, such as during upright posture, in humans. Fifty healthy individuals underwent right heart catheterization to measure pulmonary capillary wedge (PCWP) and right atrial pressure (RAP). To evaluate the effects of pericardial constraint on hemodynamics, transmural filling pressure (LV TMP) was defined as PCWP-RAP. Beat-to-beat blood pressure (BP) waveforms were recorded, and stroke volume (SV) was derived from the Modelflow method. After measurements at −30 mmHg lower body negative pressure (LBNP), which approximates the upright position, LBNP was released, and beat-to-beat measurements were performed for 15 heartbeats. At −30 mmHg LBNP, RAP and PCWP were significantly decreased. During the first six beats of LBNP release, heart rate (HR) was unchanged, while BP increased from the fourth beat. RAP increased several beats faster than PCWP resulting in an acute decrease in LV TMP from the fourth beat. A corresponding drop in SV by 3% was observed with no change in pulse pressure. From the 7th to 15th beats, LV TMP and SV increased steadily, followed by a decreased HR due to the baroreflex. A decreased TMP, but not PCWP, caused a transient drop in SV with no changes in HR or pulse pressure during LBNP release. These results suggest that the pericardium constrains LV filling during LBNP release, enough to cause a small but significant drop of SV, even at low cardiac filling pressure in healthy humans.

Effects of pericardial constraint and ventricular interaction on LV hemodynamics, including cardiac filling pressure, LV temporary pressure (LV TMP), and SV for 15 cardiac cycles.

METHODS

Subject Population

Fifty healthy volunteers (age range: 36 to 74 yr) were enrolled as part of a larger study. Subjects were excluded if they exercised for >30 min/day and >3 times/wk. All subjects were rigorously screened for comorbidities, including valvular heart disease, pericardial disease, pulmonary disease, obesity (body mass index > 30 kg/m²), hypertension, or coronary artery disease with a careful history, physical examination, 12-lead electrocardiogram, and echocardiogram including after maximal exercise testing. All subjects were informed of the purpose and procedures used in the study and signed an informed consent form, which was approved by the Institutional Review Board.
Review Boards of the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas.

Measurements

Heart rate and BP. Heart rate (HR) was determined from a three-lead electrocardiogram, and a continuous arterial BP waveform was recorded noninvasively using finger photoplethysmography. Arm cuff BP was measured by electrophysiomannometer (model 4240; SunTech Medical Instruments, Raleigh, NC) with a microphone placed over the brachial artery to detect Korotkoff sounds, and the finger arterial BP was calibrated against the cuff BP to account for peripheral pulse wave amplification.

Cardiac filling pressures. A 6-Fr Swan-Ganz catheter was placed from a peripheral antecubital vein under fluoroscopic guidance to measure pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP). Correct position of the Swan-Ganz catheter was confirmed by fluoroscopy and by the presence of characteristic pressure waveforms. The mean PCWP was used as a measure of LV end-diastolic pressure and RAP as that of pericardial pressure (30, 38). To evaluate the effects of external constraints on hemodynamics during LBNP release, LVTMP, which is the distending pressure for the LV, was calculated as PCWP − RAP as previously described (3, 5). This equation originated from physiological experiments using a pericardial flat balloon, which measures pericardial “surface pressure.” Pericardial “surface pressure” is different from pericardial “liquid pressure” measured by an open-ended catheter (34). The difference between these two pericardial pressures is the compressive contact stress developed between the surfaces (34). LV end-diastolic pressure is the sum of the LVTMP and the pressure due to external contact stress developed between the surfaces (34).

Cardiac filling pressures were referenced to atmospheric pressures, with the pressure transducer (Transpac IV; CIVCO Medical Instruments, Kalona, IA) zero reading set at 5 cm below the sternal angle in the resting supine position (Baseline). Steady-state PCWP and RAP at baseline and during −30 mmHg LBNP were measured at the end of expiration with a quiet breath hold. Beat-to-beat mean PCWP and RAP were also measured after LBNP release for 15 heart beats.

Modelflow method. A continuous finger BP waveform were recorded during the study (13, 21), and beat-to-beat systolic and diastolic BP and pulse pressure were derived from computer software (Beatfast Modelflow program, BeatScope 1.1a; Finapres Medical System BV, Amsterdam, The Netherlands). The Modelflow method allows for the accurate calculation of beat-to-beat SV (12, 42), including during changes in cardiac loading conditions such as postural stress and exercise (6).

Hemodynamic variables. Steady-state cardiac output and SV were measured at baseline and −30 mmHg LBNP by thermodilution (9). Modelflow SV at −30 mmHg LBNP was calibrated against the thermodilution method during steady-state −30 mmHg LBNP as previously reported (6, 24, 31, 45). During LBNP release, beat-to-beat finger pressure waveforms were recorded (21). The ratio of beat-to-beat SV to pulse pressure was determined to evaluate the effect of LBNP release on aortic properties.

Experimental Protocol

All measurements were performed in the fasting state in a quiet and environmentally controlled laboratory. The subject was placed in a Plexiglas LBNP tank sealed at the level of iliac crests in the supine position. After ≥30 min of quiet rest, baseline data were collected for 6 min, followed by measurements of baseline PCWP and RAP. After these measurements, −15 mmHg LBNP was provided for 6 min as part of a larger study, and then suction was increased to −30 mmHg LBNP. Steady-state data at −30 mmHg LBNP were collected from the 4th to the end of the 6th minute, followed by measurements of cardiac filling pressures at −30 mmHg LBNP. Then LBNP was released at the end of expiration with a quiet breath hold for 15 cardiac cycles during which beat-to-beat data including cardiac filling pressures were recorded.

Data Analysis and Statistics

Arterial finger BP and cardiac filling pressure waveforms were digitized through 16-bit analog to digital conversion, stored in a laboratory computer at 200 Hz, and processed with a commercial program for beat-to-beat mean PCWP and RAP detection (Biopac System, Santa Barbara, CA). Steady-state hemodynamic data at baseline and during −30 mmHg LBNP were compared by using a paired t-test, or nonparametric Man-Whitney rank sum test as appropriate. Variables after LBNP release were analyzed using Friedman one-way repeated-measures of ANOVA on ranks (nonparametric test). Dunn’s method was used in a post hoc analysis for multiple comparisons vs. the first beat at the release of LBNP. For ease of description, the time course of LBNP release was divided into two phases; early phase (first 6 beats) and late phase (7th to 15th beat). A P value <0.05 was considered statistically significant. All statistical analysis was performed using SigmaStat (Systat Software), and data are presented as means ± SD in Table 1.

RESULTS

Subject Characteristics

There were 50 healthy subjects (23 men, 27 women) in the present study. The average age of our subjects was 55 ± 11 yr with a range of 36 to 74 yr. They were 172 ± 10 cm in height, 73 ± 13 kg in body weight, and 24 ± 3.1 kg/m² in body mass index.

Steady-State Hemodynamics at Baseline and −30 mmHg LBNP

Steady-state hemodynamic data are shown in Table 1. HR increased by 10 beats at −30 mmHg LBNP compared with baseline (P < 0.001), while systolic and diastolic BP, RAP (8.0 ± 1.9 vs. 2.9 ± 1.3 mmHg; P < 0.001), and PCWP (11.4 ± 2.3 vs. 4.6 ± 1.8 mmHg; P < 0.001) significantly decreased at −30 mmHg LBNP. Cardiac output and SV at −30 mmHg LBNP were smaller than those at baseline (P < 0.001),
Hemodynamic Changes at the Early Phase of LBNP Release (First 6 Beats)

Figure 1 demonstrates an original tracing of beat-to-beat arterial pressure, HR, and cardiac filling pressure during LBNP release from one subject. LBNP release resulted in a prominent increase in RAP ($P < 0.001$) and PCWP ($P < 0.001$) (Figure 2). The increase in RAP was larger than that of PCWP, resulting in a prominent decrease in LVTMP, which reached its lowest value at the fourth beat (LVTMP 0.1 mmHg). A corresponding drop in SV by 3% (52.2 ± 18.1 vs. 50.5 ± 17.3 ml; $P < 0.05$) and cardiac output was observed at the fourth beat; however, there was no change in HR or pulse pressure (Fig. 3 and 4). The effect of external constraint on LV end-diastolic pressure was the greatest at the 5th beat after LBNP release (98 ± 19%) and gradually decreased until the 15th beat after LBNP release (81 ± 15%). After the fourth beat, SV steadily increased and returned to the pre-LBNP release level by the sixth beat. Systolic and diastolic BP increased throughout the early phase. The ratio of beat-to-beat SV to pulse pressure decreased from the fourth beat (Fig. 4).

Hemodynamic Changes at the Late Phase of LBNP Release (7th ~ 15th Beat)

RAP reached a plateau at the 8th beat, while PCWP continued to increase, resulting in a higher LVTMP at the 13th ~ 15th beat compared with pre-LBNP release (Fig. 2). HR declined during the late phase and reached its lowest value at the 12th beat (68 ± 8 beats/min), and although it started to increase after this point, it remained lower compared with pre-LBNP release at the 15th beat (75 ± 11 vs. 69 ± 9 beats/min; $P < 0.05$; Figs. 3 and 4). SV increased steadily during the late phase of LBNP release, resulting in a 20% larger SV at the 15th beat compared with pre-LBNP release (51.4 ± 13.2 vs. 61.5 ± 17.8 ml; $P < 0.05$). As the change in SV was greater than that in HR, cardiac output continued to increase during the late phase of LBNP release and achieved statistical significance at the end of the late phase (11th beat; Fig. 3). Systolic and diastolic BPs gradually decreased due to the baroreflex. The ratio of beat-to-beat SV to pulse pressure
was lowest at the seventh beat and then increased throughout the late phase of LBNP release (Fig. 4).

Preload and SV Relations During LBNP Release

Preload (LVTMP and PCWP) and SV at baseline, −15 mmHg LBNP, and during −30 mmHg LBNP release were plotted (Fig. 5). Overall LVTMP-SV relations were highly linear ($R^2 = 0.70$); however, PCWP-SV relations were not ($R^2 = 0.22$), especially when the early phase of LBNP release was included in the regression. These results may suggest that LVTMP but not PCWP is a determinant of SV during acute increases in preload in the unloaded heart. While average LVTMP at the first and the ninth beats were same, SV at the ninth beat was larger than that at the first beat. When examined carefully, the LVTMP-SV relation during the late phase of LBNP release seemed to be different from that during first four beats.

Fig. 3. Beat-to-beat heart rate, stroke volume (SV), and cardiac output during LBNP release. B1, baseline; B5–B15, the 5th through 15th heart beats after LBNP release. Early phase, first 6 beats; Late phase, from 7th to 15th beat. Values are expressed as median and 25th as well as 75th percentile. *$P < 0.05$, compared with B1.

Fig. 4. Beat-to-beat systolic BP, diastolic BP, pulse pressure, and the ratio of SV to pulse pressure during LBNP release. B1, baseline; B5–B15, the 5th through 15th heart beats after LBNP release. Early phase, first 6 beats; Late phase, from 7th to 15th beat. Values are expressed as median and 25th as well as 75th percentile. *$P < 0.05$, compared with B1.
beats after LBNP release, with the findings of steeper (individual slope 3.2 ± 2.8 vs. 1.3 ± 3.1 ml/mmHg; P < 0.01) and upward shifts of the LVTMP-SV relations during the late phase of LBNP release, perhaps due to hysteresis or due to a differential relative effect of pericardial constraint vs. ventricular interaction.

DISCUSSION

The major finding of the present study was that during cardiac unloading approximating the upright posture, an acute increase in central blood volume led to transient decreases in both LVTMP and SV. These findings suggest that the pericardium provides some constraint to LV filling even at low cardiac filling pressure in healthy humans.

Effects of Pericardial Constraint and Ventricular Interaction on LV Hemodynamics in Healthy Humans

Pericardial constraint has been studied in animals with increased cardiac volumes and pressures by use of LV pressure-volume curves (15, 16, 28, 29). In humans, Dauterman et al. (11) demonstrated that preload reduction by inferior vena cava occlusion shifted the LV pressure-volume curve downwards, which was caused by a reduction of external LV constraint. Although the LV pressure-volume curve has been extensively used to assess hemodynamics, this method requires an invasive procedure and is less able to track the dynamic beat-to-beat changes in LV SV. In the present study, we examined the effect of pericardial constraint and ventricular interaction on LV hemodynamics by beat-to-beat SV using the Modelflow method and LVTMP during −30 mmHg LBNP release in healthy subjects.

To accurately calculate end-diastolic LVTMP, the pressure surrounding the LV (pericardial and right ventricular pressure) must be subtracted from LV end-diastolic pressure (30). However, it is difficult to assess LVTMP in healthy human subjects, due to the difficulty in measuring intrapericardial pressure. It has been shown by use of a pericardial flat balloon that the right ventricular TMP was nearly zero and that pericardial “surface” pressure was proportional and similar in magnitude to the mean RAP throughout a wide range of filling pressures (8, 19, 38). Therefore, LVTMP could be defined as LV end-diastolic pressure (or PCWP) − RAP as previously reported (3, 5, 30).

Based on previous studies assessing pericardial pressure in animal models, the effects of pericardial constraint and ventricular interaction on LV volume have been extensively studied. For example, Applegate et al. (2) reported in euvolemic dogs that there was no pericardial constraint on LV hemodynamics in the resting supine position. This group also showed that the LV was smaller during a large volume infusion (1,000 ml) compared with baseline or during a low dose volume infusion (500 ml) when the pericardium was intact (1), suggesting that the effect of pericardial constraint on LV volume was significant at larger cardiac volumes.

In addition, Moore et al. (30) examined the effects of pericardial constraint and ventricular interaction on SV and reported that volume loading in dogs with heart failure increased RAP more than LV end-diastolic pressure, resulting in decreases in LVTMP and SV presumably due to pericardial constraint. Kroeker et al. (25) also showed that rapid volume injection into the right atrium in dogs with normal filling pressures increased right ventricular SV and end-diastolic pressure immediately, which induced compensatory decreases in LVTMP and SV.

Similar to these previous studies, we observed a decrease in LVTMP and an increase in PCWP during the initial several beats after LBNP release. As it takes the blood entering the right atrium at least several beats to get to the left side of the heart after LBNP release (37, 43), the acute increase in PCWP is likely due to pericardial constraint. A decrease in LVTMP and a corresponding drop of SV also suggests that pericardial constraint and consequent ventricular interaction play a role in modulating LV hemodynamics even at a low cardiac filling pressure in healthy subjects.

Fig. 5. Preload vs. SV relations at baseline and −15 mmHg LBNP, and −30 mmHg LBNP release. ●, LVTMP; ○, PCWP.
Cardiac Filling Pressures at the Onset of Pericardial Constraint in Healthy Humans

Applegate et al. (2) reported in dogs during volume infusion that pericardial constraint occurred when LV end-diastolic pressure was 9.1 ± 2.9 mmHg and right ventricular end-diastolic pressure was 4.1 ± 2.9 mmHg. Kroeker et al. (25) also showed in dogs during rapid blood injection that the modulation of LVTMP and SV by pericardial constraint was diminished when RAP was <5 mmHg. In the present study, we observed the lowest SV at the fourth beat, at which time the average PCWP was 8.1 ± 2.2 mmHg and RAP was 7.6 ± 2.0 mmHg. These results seem to confirm and extend the previous findings showing pericardial constraint at low cardiac filling pressures in animal models to healthy humans.

These results, however, might not be applicable to healthy subjects of all ages. Young adults seem to have a more compliant pericardium and myocardium than sedentary older adults (3). Endurance athletes are also reported to have a more compliant and larger LV (27), probably due to volume and/or pressure overload to the heart during exercise training (33). Therefore, their pericardium may be more compliant and/or larger. The mean age of our subjects was 55 ± 11 yr with a range of 36 to 74 yr. Therefore, the results may differ if we enrolled only young subjects or endurance athletes who may have a more compliant pericardium.

Hemodynamic Changes During the Early Phase of LBNP Release

We observed a significant but transient decrease in LVTMP and SV probably due to pericardial constraint and right ventricular-LV interaction. This decrease in the SV during LBNP release was consistent with previous findings that measured beat-to-beat SV by echo Doppler at the high ascending aorta without measurements of cardiac filling pressures (21).

The −30 mmHg LBNP reduced preload significantly with low PCWP (4.6 ± 1.8 mmHg) and RAP (2.9 ± 1.3 mmHg). These changes in filling pressure are similar to those during 60° head-up tilt (41). If we apply these results to clinical settings, a postural change from the upright to the supine position does decrease SV during the first several seconds in most patients with normal or increased preload. Patients with heart failure (23), right ventricular infarction (17), and cardiac tamponade (7) have higher cardiac filling pressures, and their hemodynamics may be more influenced by pericardial constraint compared with healthy subjects. Therefore, hemodynamic conditions in these patients may deteriorate during positional changes from the upright to the supine position because of the possible effects of pericardial constraint on LV hemodynamics. Therefore, assessing the reduction in SV during a postural change from the upright to the supine position may identify patients with a higher risk for hemodynamic decompensation from those with a low risk.

Effects of Ventricular Interaction on LV Hemodynamics During the Early Phase of LBNP

Because the ventricles share a ventricular septum, there is a direct interaction between the two ventricles through the ventricular septum or through the direct connections of the LV and right ventricular free walls. Previous studies examined the effects of ventricular interaction on LV hemodynamics with and without an intact pericardium. For example, Janicki and Weber (22) observed diastolic ventricular interaction over a wide range of filling pressure in all dogs with and without a pericardium although the magnitude of the ventricular interaction was significantly larger when the pericardium was present. Santamore et al. (32) examined the changes in LV end-diastolic pressure in dogs by changing right ventricular pressure while pericardial pressure was maintained constant. They found that there was an increase in LV end-diastolic pressure by changing right ventricular pressure even when pericardial pressure was maintained at zero or very low. The increase in LV end-diastolic pressure due to ventricular interaction was greater when right ventricular end-diastolic pressure was high and was smaller when right ventricular pressure was low. There was only a very small increase in LV end-diastolic pressure (−1 mmHg) when right ventricular end-diastolic pressure was increased from 0 to 5 mmHg (32). These results suggest that ventricular interaction does exist even at low cardiac filling pressure although its effect on LV end-diastolic pressure seems to be very small when mechanical disequilibrium between the ventricles and pericardium occurs.

In the present study, the estimation of LVTMP from PCWP and RAP relies on previous findings that the pericardial pressure was similar to RAP over a wide range of cardiac filling pressure (38). We observed that during the first two beats (from 1st to 3rd beat) after LBNP release, PCWP significantly increased by 2.3 ± 0.4 mmHg while RAP increased from 2.9 ± 0.2 to 5.9 ± 0.2 mmHg. The significant increase in PCWP during the first two beats after LBNP release may suggest that hemodynamic changes during the early phase of LBNP release were not exerted by ventricular interaction itself but by the combination of pericardial constraint and ventricular interaction. Therefore, it is likely that the ventricles and the pericardium were in an equilibrium state just after LBNP release.

One may argue that a mechanical disequilibrium between ventricles and the pericardium occur during −30 mmHg LBNP and that the pericardial pressure may not be the same as the RAP. To address this concern, we modeled that pericardial pressure was zero at the first beat, a half of RAP at the second beat, and the same as RAP at the third beat after LBNP release as we demonstrated that an equilibrium state seemed to exist at the third beat after LBNP release. Then, we used the equation of LVTMP = PCWP − (1/3 * PCWP + 2/3 * pericardial pressure) by Mirsky and Rankin (29). In this model, estimated LVTMP significantly decreased from the 3rd beat to the 11th beat after LBNP release with the lowest value at the 5th beat, which seemed to be related to the decrease in SV at the 4th beat. However, modeled LVTMP at the 15th beat was not higher than that at the 1st beat after LBNP release although SV and PCWP significantly increased by that point. These findings may suggest that 1) the pericardial pressure at the first beat was not zero, and 2) the pressure gradient between RAP and pericardial pressure was very small.

Hemodynamic Changes During the Late Phase of LBNP Release

We observed a gradual increase in SV throughout the late phase of LBNP release, and SV did not reach a plateau at the 15th beat (average 12.6 s after LBNP release). Contrary to the
present results, Toska and Walløe (37) reported that SV increased and reached a plateau within 10 s after transition from 30° head-up tilt to the supine position in healthy subjects. As we performed −30 mmHg LBNP, which causes hemodynamics changes similar to those by 60° head-up tilt (41), the blood shifted in the lower body could be larger in the present study than in the previous study. The different time course of the increase in the SV may be due to the difference in the blood volume, which shifted in the lower body and then entered the right atrium after the termination of head-up tilt or LBNP.

Mechanical Effect of LBNP on BP

Systolic and diastolic BP increased prominently without any changes in HR or SV after LBNP release and reached conventional statistical significance within a few cardiac cycles. A substantial increase in mean BP (16%, 13 mmHg) immediately after LBNP release was also observed by Hisdal et al. (21). Conversely, LBNP decreases BP measured by a finger BP cuff within seconds with or without increases in HR (13, 20, 21).

LBNP decreases gastric pressure or intra-abdominal pressure in humans (44). Valenza et al. (39) also reported that intra-abdominal and intrathoracic pressures were decreased by negative extra-abdominal pressure in dogs. Based on these previous findings, we speculate that the application of LBNP in humans can similarly decrease intrathoracic and intra-abdominal pressures, while LBNP release can cause a transient relative increase in intrathoracic and intra-abdominal pressures. This relative increase in intra-abdominal and intrathoracic pressures during LBNP release may mechanically compress the aorta and cause a transient increase in BP with no changes in HR or SV. The findings that the ratio of beat-to-beat SV to pulse pressure decreased from the 4th to 12th beat may also suggest that the mechanical load to the aorta subsequent to LBNP release changed aortic properties and induced increases in systolic and diastolic pressures just after LBNP release. This increase in BP may partly contribute to the increase in PCWP because an increase in afterload to the LV might impede LV ejection and elevate LV end-diastolic pressure.

We observed no change in pulse pressure during the early phase of LBNP release, although there was a transient drop in SV. Pulse pressure is regulated by the interaction of SV and the properties of the arterial system (10). Therefore, we speculate that the effect of a decreased SV on pulse pressure may have been offset by that of an increased arterial stiffness due to the mechanical load to the aorta during the early phase of LBNP release.

Study Limitations

First, SV obtained by the Modelflow method has not been shown to be exactly the same as those by a “gold standard” method (6, 26, 31). However, there are no “gold standard” methods for measuring beat-to-beat SV. There may be small differences between beat-to-beat SV measured by the Modelflow method and that by echocardiography when head-up tilt is applied or aortic compliance is altered (40, 42). However, these differences in beat-to-beat SV by two methods are systematic (40). Therefore, the Modelflow method is a useful technique to track the changes in beat-to-beat SV in the present study. Second, changes in LVTMP were correlated to those in SV during LBNP release better than PCWP, while the LVTMP-SV relation during the late phase of LBNP release was steeper and shifted upward compared with that during the first four beats. This upward shift of the relation may have been due to hysteresis, or due to a differential relative magnitude of pericardial constraint vs. ventricular interaction, or due to measurement errors by the Modelflow method. Third, our results did not include LV volumes during LBNP release for 15 cardiac cycles. LV volume data during LBNP release could give very useful information for understanding the hemodynamics during LBNP. However, it is sometimes difficult to obtain good LV images by echocardiography during LBNP release because the heart position is being shifted upward during the release.

Conclusions

We demonstrated that a decrease in LVTMP, but not PCWP, caused a transient drop of SV with no changes in HR or pulse pressure during LBNP release. These results suggest that the pericardium provides constraint to LV filling during LBNP release, which is large enough to cause a small but significant drop of SV, even at low cardiac filling pressure in healthy humans.

GRANTS

This study was supported by National Institutes of Health Grant AG-17479-02 and American Heart Association Postdoctoral Fellowship Grant 09POST2050083.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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HEMODYNAMICS DURING CARDIOVASCULAR UNLOADING.


