Evaluation of alterations on mitral annulus velocities, strain, and strain rates due to abrupt changes in preload elicited by parabolic flight

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Caiani EG, Weinert L, Takeuchi M, Veronesi F, Sugeng L, Corsi C, Capderou A, Cerutti S, Vaida P, Lang RM. Evaluation of alterations on mitral annulus velocities, strain, and strain rates due to abrupt changes in preload elicited by parabolic flight. J Appl Physiol 103: 80–87, 2007; doi:10.1152/japplphysiol.00625.2006.—We tested the hypothesis that in normal subjects, cardiac tissue velocities, strain, and strain rates (SR), measured by Doppler tissue echocardiography (DTE), are preload dependent. To accomplish it, immediately preceding image acquisition, reversible, repeatable, acute nonpharmacological changes in preload were induced by parabolic flight. DTE has been proposed as a new approach to assess left ventricular regional myocardial function by computing tissue velocities, strain, and SR. However, preload dependence of these parameters in normal subjects still remains controversial. DTE images (Philips) were obtained in 10 normal subjects in standing upright position at normogravity (1 G) and hypergravity (1.8 G) and in microgravity (0 G), and with −50 mmHg lower body negative pressure (LBNP). Myocardial velocity curves in the basal interventricular septum were reconstructed offline from DTE images, from which peak systolic (S), early (E) and late (A) diastolic velocities, SR, and peak systolic strain (PSε) were measured and averaged over four beats. At 1.8 G (reduced venous return), S, E, and A decreased by 21%, 26%, and respectively, compared with 1-G values, while at 0 G (augmented venous return), E, A, and PSε increased by 57%, 53%, and 49%, respectively. LBNP reduced E and PSε. In conclusion, our results were in agreement with those obtained in animal models, in which preload was changed in a controlled, acute, and reversible manner, and image acquisition was performed immediately following preload modifications. The hypothesis of preload dependence was confirmed for S, E, A, and PSε, while SR appeared to be preload independent, probably reflecting intrinsic myocardial properties.

Doppler tissue echocardiography; preload dependence; real-time three-dimensional echocardiography; weightlessness

DOPPLER TISSUE ECHOCARDIOGRAPHY (DTE) has been widely used in clinical practice to provide noninvasive information on regional left ventricular (LV) systolic and diastolic function (3, 16, 20, 21, 25, 27) and on filling pressures (8, 12, 14, 15, 17) and to measure mechanical synchronicity (30). By using this imaging modality, regional longitudinal myocardial tissue contraction and relaxation velocities, as well as one-dimensional strain (ε) and strain rate (SR), can be quantified and used as indexes of regional function.

The mitral annulus motion represents changes in longitudinal LV long-axis dimension, which could reflect LV volume changes. In the clinical evaluation of ventricular function, assessment of the rate of change in LV volume, rather than the absolute change, is desirable, since it is assumed that an abnormality reflected in the long-axis dimension could be evident earlier than the clinical manifestation of global LV abnormality. DTE provides this information, as it has the capability of recording the low velocities of the moving mitral annulus with a high sampling rate. However, myocardial tissue velocities are influenced by tethering and passive rigid motion of adjacent structures. Myocardial ε represents the deformation of myocardial tissue after application of a force: it represents a promising measure of long-axis contractility and is uninfluenced by tethering and passive rigid motion (7). SR, the temporal derivative of ε, is the rate (i.e., velocity) of the tissue deformation.

Besides their potential clinical utility, the load dependence of these parameters remains controversial. In fact, there is a large number of studies that have investigated the load dependency of tissue velocity, ε, and SR indexes using a variety of maneuvers to alter preload [i.e., saline loading, changes in posture, lower body negative pressure (LBNP), pharmacological maneuvers, blood volume reduction] that have provided contradictory results (1–3, 8, 10, 11, 19, 20, 26, 29). We hypothesized that such discrepancies in previous results were due to the implemented experimental protocols, in which preload alterations were induced in different magnitudes and rates, and image acquisition was performed several minutes after preload change. This could have enabled a variety of physiological compensatory mechanisms to operate, thus introducing confounding variables in the measured indexes. In fact, previous studies performed in animal models (12, 23, 25, 28), in which the experimental protocol included image acquisition immediately following acute changes in preload, evidenced a preload dependence in DTE parameters, which appear to contradict the results of some studies performed in humans.

Following these considerations, we hypothesized that, in healthy subjects, DTE parameters (i.e., regional longitudinal myocardial tissue contraction and relaxation velocities, ε, and SR) are not preload independent. Specifically, we expected the
DTE parameters to decrease in keeping with preload reduction and to increase when preload is augmented, an observation that is in agreement with previous animal studies. Accordingly, the aim of this paper was to test this hypothesis by using an experimental maneuver such as parabolic flight, able to induce acute, reversible, repeatable, nonpharmacological changes in preload, and by acquiring DTE images immediately following the preload change, thus minimizing the introduction of compensatory mechanisms that could have affected previous human studies.

Parabolic flight represents a unique experimental setup to evaluate the immediate physiological adaptations of the cardiovascular system to different gravity (head to foot; Gz) levels obtained during the parabola (normogravity, 1 Gz; hypergravity, 1.8 Gz; microgravity, 0 Gz). Parabolic flights were chosen to test our hypothesis of preload dependency of DTE because 1) they are known to generate abrupt changes in hydrostatic pressure gradients, which are greater in magnitude than those induced by other maneuvers, such as posture changes, water immersion, passive body tilting, LBNP; 2) both a reduction and an increase in preload can be induced using the same experimental settings; 3) the subject can be studied in standing position; 4) cardiac ultrasound imaging can be performed immediately following the preload alteration; and 5) changes in load can be performed reliably in a repeated fashion. Moreover, the increase in venous return elicited at 0 Gz by parabolic flight is accompanied by the nullification of the intraventricular pressure gradient (18). The application of LBNP in this particular condition allows the unique opportunity to investigate the effects of a reduction in preload without the presence of intervening intraventricular hydrostatic pressure gradients.

On the basis of these considerations, we studied the effects on DTE parameters of 1) acute preload reduction during 1.8 Gz; 2) acute preload increase during 0 Gz; and 3) combined effects of microgravity and reduction in venous return, induced by LBNP at −50 mmHg applied during 0 Gz.

METHODS

Subjects. Ten normal volunteers (8 men, mean age 38 ± 11 yr, mean weight 68 ± 11 kg, mean height 176 ± 11 cm) without a history of cardiovascular disease were enrolled in the study after providing written informed consent. All subjects underwent a Joint Aviation Administration Flight Crew Licensing 3-Class 2 (private pilot) physical aptitude test, which included ECG examination, blood pressure measurements, blood sample tests, and other cardiopulmonary examinations when required. Moreover, the day before the flight every subject underwent a standard echocardiographic examination, which exhibited a normal LV function and no evidence of valvular heart disease. All subjects were screened before participation to ensure adequate acoustic windows, even when echocardiographic imaging was performed in the upright position. None of the subjects was taking medication before and/or during the flights. This study was approved by the European Space Agency (ESA) ethics committee.

Equipment and image acquisition. The study was conducted during the 41st ESA parabolic flight campaign (November 2005) on board the Zero-G Airbus A300 aircraft in Bordeaux, France. Each flight lasted 2.5–3 h and included 31 parabolas. The cabin pressure and temperature were maintained around 800 mbar and between 18 and 25°C, respectively, during parabolic maneuvers.

Gz variations during a parabolic flight trajectory include four consecutive phases: I) 1 Gz, before parabola initiation; II) 1.8 Gz, during the ascending phase of the parabola (20 s); III) 0 Gz, at the top of the parabola (24 s); and IV) a second 1.8-Gz period, during the descending phase of the parabola (20 s). Between consecutive parabolas, a steady-state period (at 1 Gz) was maintained for a minimum of 2 min. Instantaneous Gz was continuously measured using the aircraft’s accelerometer.

Each subject was imaged in the upright standing position during a maximum of 10 consecutive parabolas, with the abdomen and lower extremities placed inside a LBNP chamber. To allow the lower limbs to stay relaxed (to maximize blood and fluid movement to/from the lower body), subjects were placed on a saddle within the LBNP chamber, with the arms secured to the structure by straps. To test the effect of reduction of venous return while in weightlessness, a negative pressure of −50 mmHg was applied during 0 Gz, in selected parabolas in a random order.

Imaging was performed from the apical window using a iE33 system (Philips Medical System, Andover, MA). To avoid data acquisition during each Gz-change transition along the parabola, data sets were collected at 1 Gz, 10 s before the initiation of phase II, and at 1.8 Gz and 0 Gz, 5 s after the beginning of phases II and III, respectively. To minimize changes in intrathoracic pressure, data acquisition was performed during a breath hold, while avoiding the Mueller or Valsalva maneuvers. To avoid body movements, both subject and sonographer were stabilized against free floating. A second operator aided in optimizing image quality.

Real-time color Doppler tissue myocardial velocities were acquired from the apical four-chamber view, using a S5 broadband transducer, from the same intercostal space during all the phases of the parabola. To minimize the angle between the beam and the direction of annular motion, care was taken to keep the ultrasound beam perpendicular to the annulus plane. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation. Sector size and depth were set to obtain high frame rate (95 ± 5 frames/s). For each gravity level in the parabola, four consecutive beats were collected and stored in a cine-loop format.

In addition, transthoracic real-time three-dimensional echocardiography (RT3DE) was performed with a full-matrix array transducer (X3, 2–4 MHz) in the harmonic mode. For each gravity level in the parabola, one RT3DE data set (frame rate 20 Hz) was acquired using the wide-angled acquisition modality, in which four wedge-shaped subvolumes (93° × 21°) are obtained over four consecutive cardiac cycles with ECG gating. Care was taken to include the entire LV within the pyramidal three-dimensional scan volume.

Data analysis. The DTE and RT3DE data sets acquired in each subject during phases I, II, and III of the parabola (i.e., 1 Gz, 1.8 Gz, and 0 Gz) were first visually inspected. Parabolas with adequate image quality in all phases were selected for offline analysis, performed randomly by an expert reader blinded to the subject’s identity and gravity phase.

DTE data sets were analyzed using commercially available software (SQ module, Qlab, version 4.2). Regional myocardial velocity curves (9) were reconstituted offline from the apical four-chamber DTE color images, using a region of interest (ROI) placed in the basal interventricular septum (IVS). To ensure that measurements reflected motion of the same tissue segment throughout the cardiac cycle, the ROI position was manually adjusted, frame by frame. The regional SR curve in the IVS segment was then estimated from the spatial derivative of myocardial velocity over the user-defined computation area (10-mm-length M-mode line, oriented from base to apex). Regional ε was then derived by time integration of the SR curve (7) and expressed as percentage of deformation with respect to its end-diastolic length.

From these curves, the following parameters were measured in four consecutive beats, and results were averaged: peak systolic (S′), early diastolic (E′) and late diastolic (A′) velocities; peak longitudinal systolic strain (PSE); and peak systolic (S′) and early diastolic (E′) and late diastolic (A′) strain rates. The E′/A′ ratio was then derived from the measured values.
To quantify LV volumes and ejection fraction (EF), RT3DE data sets were analyzed offline using previously validated custom software on the basis of semiautomated LV surface detection (4). End-systolic (ESV) and end diastolic (EDV) LV volumes were measured, and stroke volume (SV) and EF were derived from EDV and ESV values.

Statistical analysis. LV volumes and DTE-derived parameters were averaged for all subjects in each gravity phase. Data were displayed as means ± SD. One-way ANOVA with repeated measures (P < 0.05) was used to test the differences in each parameter among gravity phases. Then the Tukey test, extended to the correlated samples, was used to perform a pairwise comparison to test if a significant difference was present between the gravity phases. The effects of LBNP activated during 0 Gz on LV volumes and DTE-derived parameters were tested by paired Student’s t-test. Differences were considered significant for P < 0.05 compared with the results obtained at 0 Gz without LBNP.

RESULTS

DTE and RT3DE imaging during parabolic flights were feasible in all subjects, despite the short duration of each phase of the parabola. Both quantitative analysis of LV basal IVS motion and of LV volumes were feasible in all DTE and RT3DE data sets selected for being evaluated. The time required to analyze a complete DTE cine-loop (4 beats) was ~7 min, while the time required to compute LV EDV and ESV from a single RT3DE data set was ~3 min.

Significant changes in both heart rate (HR) and LV volumes were measured during the different phases of the parabola (Table 1). Compared with 1 Gz during hypergravity HR increased by 14% while LV EDV decreased by 21%. ESV remained unchanged, resulting in a reduction of SV of 27% with no significant changes in EF. With the increase in preload elicited by microgravity, HR decreased by 13%, and EDV and ESV increased by 23% and 10%, respectively, compared with 1 Gz. This resulted in an increase in SV of 34% with no significant changes in EF.

Figure 1 shows a representative example of LV tissue velocity (top), strain (middle), and SR (bottom) curves obtained at the base of IVS during one representative cardiac cycle in a subject during normogravity (solid line), hypergravity (dotted line) and microgravity (dashed line). Changes in the curves relevant to the gravity levels are noticeable, in particular the increase at 0 Gz in the E’ and A’ velocity peaks, as well as in PSe.

Significant changes in LV basal IVS tissue velocity were measured during the different gravity levels of the parabola (Fig. 2). At 1.8 Gz, with the reduction in preload, the IVS S’, E’, and A’ decreased by 21%, 21%, and 26%, respectively, compared with 1-Gz values. At 0 Gz, with the increase in preload, IVS E’ and A’ increased by 57% and 53%, respectively, compared with 1-Gz values; consequently, IVS E’/A’ ratio did not vary significantly with changes in gravity (Table 2).

Table 1. Mean values of HR and LV volumes computed in 10 normal subjects during the 3 different gravity conditions achieved in the parabola

<table>
<thead>
<tr>
<th></th>
<th>Phase I (1 Gz)</th>
<th>Phase II (1.8 Gz)</th>
<th>Phase III (0 Gz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>78±13</td>
<td>89±14*</td>
<td>68±12†</td>
</tr>
<tr>
<td>LV EDV, ml</td>
<td>89±27</td>
<td>70±25*</td>
<td>108±32†</td>
</tr>
<tr>
<td>LV ESV, ml</td>
<td>44±17</td>
<td>39±25</td>
<td>50±26‡</td>
</tr>
<tr>
<td>LV SV, ml</td>
<td>44±10</td>
<td>31±6*</td>
<td>58±12†</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>51±5</td>
<td>48±16</td>
<td>55±8</td>
</tr>
</tbody>
</table>

Values are means ± SD. Gravity conditions were normogravity (1 Gz), hypergravity (1.8 Gz), and microgravity (0 Gz). HR, heart rate; LV EDV, left ventricular (LV) end-diastolic volume; LV ESV, LV end-systolic volume; LV SV, LV stroke volume; LV EF, LV ejection fraction. *P < 0.05 vs. 1 Gz. †P < 0.05, 1.8 Gz, vs. 0 Gz.
Changes in LV basal IVS strain and SR parameters during the parabola are shown in Fig. 3. The PSε at 0 Gz increased significantly by 49% compared with that at 1 Gz, while S’ SR did not show significant changes. The E’ SR did not change at 1.8 Gz, while it increased by 41% at 0 Gz. Conversely, A’ SR was significantly decreased by 26% at 1.8 Gz, and no changes were observed at 0 Gz (Table 3).

With the activation of the LBNP countermeasure during microgravity, HR and LV volumes trended toward 1-Gz values, resulting in an attenuation of the changes noted at 0 Gz without the use of LBNP. In particular, HR was 74 ± 17 beats/min [P: not significant (NS)], ESV was 43 ± 14 ml (P: NS), and EDV and SV were found restored to 1-Gz values: in fact, they were significantly reduced compared with 0 Gz without the LBNP applied (86 ± 21 and 42 ± 9 ml, respectively) and comparable (−3% and −5%, respectively) to 1-Gz values. In addition, E’ and PSε were found significantly decreased in the IVS segment (5.0 ± 0.8 cm/s and 13.3 ± 6.4%, respectively) at 0 Gz, when LBNP was applied (Fig. 4), resulting in only +2% and +5%, respectively, compared with 1 Gz.

On the contrary, A’ did not change (5.1 ± 1.2 cm/s) with LBNP, thus remaining increased compared with 1 Gz (±27%); this resulted in a significant decrease in E’/A’ (1.0 ± 0.3 arbitrary units, −33% compared with 1 Gz). Also, the SR parameters did not change with 0 Gz and LBNP (SR S’: −1.2 ± 0.7 s−1; SR E’: 1.7 ± 1.0 s−1; SR A’: 1.2 ± 0.3 s−1), resulting in E’ SR still increased (+41%) compared with the 1-Gz value.

**Table 2. Mean values of the tissue velocity parameters (peak systolic, peak early diastolic, and peak late diastolic) measured in the basal interventricular septum in 10 normal subjects during the 3 different gravity conditions achieved in the parabola**

<table>
<thead>
<tr>
<th></th>
<th>Phase I (1 Gz)</th>
<th>Phase II (1.8 Gz)</th>
<th>Phase III (0 Gz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S’, cm/s</td>
<td>6.3±1.5</td>
<td>4.9±1.0*</td>
<td>6.2±1.5†</td>
</tr>
<tr>
<td>E’, cm/s</td>
<td>4.9±1.4</td>
<td>3.7±1.0*</td>
<td>7.4±1.6†</td>
</tr>
<tr>
<td>A’, cm/s</td>
<td>4.0±1.7</td>
<td>2.8±1.2*</td>
<td>5.5±1.3†</td>
</tr>
<tr>
<td>A’/E’, au</td>
<td>1.5±0.9</td>
<td>1.5±0.7</td>
<td>1.4±0.5</td>
</tr>
</tbody>
</table>

Values are means ± SD. S’, E’, and A’ are peak systolic, peak early diastolic, and peak late diastolic tissue velocities, respectively; au, arbitrary units. *P < 0.05 vs. 1 Gz, †P < 0.05, 1.8 Gz vs. 0 Gz.

**DISCUSSION**

Several studies have been performed in the attempt to define the load dependency of pulsed Doppler tissue and two-dimensional color DTE imaging-derived parameters (longitudinal tissue velocity, strain, and SR), but results have been often contradictory. In our study, we used parabolic flight to induce reversible and repeatable acute nonpharmacologically induced variations in preload in the same subject associated with changes in gravitational acceleration and thus test the hypothesis of load dependence of DTE parameters.

The parabolic flight experimental condition is known to result in abrupt changes in hydrostatic pressure that affect the cardiovascular system by causing fluid shifts from the lower extremities toward the head and thorax, and vice versa (13). Specifically, at 0 Gz, the increase in cardiac volumes that occurs secondary to the increase in central blood volume happens despite a decrease in central venous pressure compared with atmospheric pressure (24). Central transmural pressure in the right atrium decreases, which is in accordance with the increase in cardiac chamber volume.

During the parabola, also changes in intraventricular hydrostatic pressure gradients (from base to apex) occur in a subject in the standing position. The intraventricular hydrostatic pressure difference, ΔP_{LV}, is equal to ρ_{blood} g Δh_{LV}, where ρ_{blood} represents the fluid density (1.060 kg/m³), g is the gravitational acceleration, and Δh_{LV} is the fluid column height from the mitral valve annulus and the apex of the left ventricle (18). Assuming Δh_{LV} equal to 0.07 m, at 1 Gz (g = 9.8 m/s²), ΔP_{LV} is ~730 Pa (=5.5 mmHg). The effect of a linearly increasing intraventricular pressure from base to apex, for a constant venous return and a given ventricular base pressure, is to augment the diastolic filling of the heart by increasing the elongation of the elastic, contractile, and viscoelastic elements of the ventricular wall. During phase II (g ~ 18 m/s²), ΔP_{LV} increases up to 10 mmHg, while during phase III (g ~ 0 m/s²), ΔP_{LV} decreases to 0 mmHg. With the activation of LBNP at ~50 mmHg during 0 Gz, it is possible to study the effects of a reduction in venous return when a null intraventricular pressure gradient is present, comparing the results with those obtained at 0 Gz with no LBNP.

Our results showed significant changes in DTE-derived parameters associated with the different phases of the parabolic flight.

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LV filling compared with 1 G cardiac filling pressure (24), which resulted in an increase in was in agreement with the augmented LA dimensions and induced preload alterations.

Conversely, at 0 G because of the unbalanced reduction in both E’ and A’ with nitroglycerin and an increase by a 40° elevation in the subject’s legs. Also, Jacques et al. (12), using an open-chest dog model and inferior vena cava occlusion, found that E’ and A’ were significantly influenced by preload. Other studies, performed in young volunteers undergoing blood donation (1), and in patients with preserved systolic function, pre-and post hemodialysis (2, 10, 11), showed a reduction in E’ and A’ only when blood fluid removal was greater than 2 kg. The IVS E’/A’ ratio, previously proposed as a possible load-independent index in normal subjects (19), was found unchanged in both 1.8 G_2 and 0 G_2, thus supporting the utility of this parameter as a relatively load-independent index of diastolic function. However, when LBNP was applied at 0 G_2, because of the unbalanced reduction in both E’ and A’, a significant modification compared with 0 G, without LBNP was noticed. Further investigations are needed to make a clear

Peak systolic velocity. We found that at 1.8 G_3 the IVS S’ velocity was reduced, in agreement with a previously reported animal model study, in which preload was reduced using a dobutamine infusion (25). Studies performed in humans, however, have reported discordant results: an increase in S’ using nitroglycerin (3); no change in S’ after hemodialysis (11) or blood donation (1); a decrease in S’ with LBNP at −40 mmHg (19). These discrepancies can be explained considering that the magnitude of preload reduction in the first two studies was smaller (i.e., LV EDV decreased by <10%) and induced over a longer interval compared with our study. Importantly, we found no changes in S’ associated with the preload increase induced at 0 G_3, which is in agreement with the study by Andersen et al. (3), who used the Trendelenberg position to induce preload alterations.

Peak diastolic velocities. As hypothesized, we found that the IVS E’ and A’ velocities were load dependent, decreasing at 1.8 G_3 and augmenting at 0 G_2. At 1.8 G_2, the changes in venous return, which reduced left atrial (LA) volumes (5), were prevailing over the expected countereffect of increased LV filling due to the augmented intraventricular pressure gradient. Conversely, at 0 G_2 with the acute disappearance of hydrostatic gradients, the observed increase in E’ and A’ velocities was in agreement with the augmented LA dimensions and cardiac filling pressure (24), which resulted in an increase in LV filling compared with 1 G_2. The activation of LBNP significantly reduced E’ but not A’. This could be expected, since during atrial systole the ventricular myocardium is passive, and its displacement is a result of the atrial “pull” on the mitral ring and of the active propagation of pressure and flow.

Our findings are in agreement with those previously reported in normal subjects studied in the left lateral decubitus position. Specifically, Firstenberg et al. (8) described a decrease in E’ using LBNP at −30 mmHg and an increase following saline infusion; Voigt et al. (26) measured a significant reduction in both E’ and A’ with nitroglycerin and an increase by a 40° elevation in the subject’s legs. Also, Jacques et al. (12), using an open-chest dog model and inferior vena cava occlusion, found that E’ and A’ were significantly influenced by preload.

Table 3. Mean values of the strain and strain rate parameters measured in the basal interventricular septum in 10 normal subjects during the 3 different gravity conditions achieved in the parabola

<table>
<thead>
<tr>
<th>Phase I (1 G_2)</th>
<th>Phase II (1.8 G_2)</th>
<th>Phase III (0 G_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS e, %</td>
<td>12.6±3.7</td>
<td>14.5±5.6</td>
</tr>
<tr>
<td>S’ SR, s⁻¹</td>
<td>-1.3±0.6</td>
<td>-1.3±0.4</td>
</tr>
<tr>
<td>E’ SR, s⁻¹</td>
<td>1.2±0.2</td>
<td>1.4±0.7</td>
</tr>
<tr>
<td>A’ SR, s⁻¹</td>
<td>1.4±0.4</td>
<td>1.0±0.4</td>
</tr>
</tbody>
</table>

Values are means ± SD. PS e, peak systolic strain; S’ SR, E’ SR, and A’ SR are peak systolic, peak early diastolic, and peak late diastolic strain rates, respectively. *P < 0.05 vs. 1 G_2.
Peak systolic strain. Our results showed that a reduction in LV EDV and SV at 1.8 Gz did not cause any significant change in PS\(\varepsilon\), whereas their increase at 0 Gz correlated with a significant increase in PS\(\varepsilon\). Also, reducing venous return by the application of LBNP at 0 Gz, thus restoring EDV and SV to the 1-Gz values, reduced PS\(\varepsilon\), supporting the hypothesis that this parameter is reflecting changes in global hemodynamic rather than changes in LV contractility. In fact, previous studies using animal models have shown that volume loading markedly increased PS\(\varepsilon\), and this could not be attributed to increased LV contractility, as indicated by the unchanged peak systolic elastance (23). These findings suggest that, for a normal myocardium, systolic strain quantifies regional systolic deformation of the LV and is mainly determined by the ejection performance, i.e., the SV (28). Also, mathematical modeling would predict an increase in PS\(\varepsilon\) with augmenting preload, as long as the contractile function is preserved (6). Conversely, recent studies performed in normal subjects have been contradictory, reporting PS\(\varepsilon\) both as a reasonably load-independent measure of LV contractility (3) or as a load-dependent parameter (1).

Peak strain rates. Previous studies showed that changes in regional S’ SR are predominantly related to local contractile function and less on loading conditions compared with systolic strain (28). We found the S’ SR to be unaffected by changes in preload, thus supporting the hypothesis that S’ SR is a preload-independent index of contractile function. The observation that diastolic E’ SR and A’ SR remained unchanged at 0 Gz, with or without LBNP, supports the hypothesis that these indexes are independent from loading conditions alone, but they could be a measure of more complex interactions between the intrinsic properties of the myocardium (i.e., stiffness, compliance, etc.) and extrinsic loading conditions applied to a tissue with variable elastic properties.

In summary, our results are in agreement with those obtained in animal models, in which preload was changed in a controlled, acute, and reversible manner, and image acquisition was performed immediately after the preload maneuver. Our hypothesis of preload dependence in DTE parameters in normal subjects was confirmed for regional longitudinal myocardial tissue contraction and relaxation velocities and PS\(\varepsilon\). In contrast, SR appeared to be influenced by more complex mechanisms.

Clinical implications. On the basis of observations suggesting a relative independence of loading conditions in patients with diastolic dysfunction (20), E’ has been used to correct for the influence of relaxation on the transmitral E velocity and to predict LV filling pressures. In fact, it has been shown, in patients who underwent right heart catheterization, that the E/E’ ratio is the most accurate index in determining pulmonary capillary wedge pressure (14). As we found E’ to be preload dependent, this implies that E/E’ is not consistently predictive of LV filling pressures in patients without underlying cardiac diseases. Moreover, this indicates that in these patients E’ could be used directly to noninvasively predict pulmonary capillary wedge pressure, in agreement with (8), rather than be independent of it. Our finding that S’ SR is preload independent confirms the hypothesis that changes in this index are probably more related to local contractile function (28), and thus it could be used to assess regional systolic dysfunction. On the contrary, the load dependence of PS\(\varepsilon\) should be taken into account when quantifying systolic regional wall deformation. These results could be of help in understanding the cardiac response in a patient with sustained increase or decrease in preload.

Limitations. This study has several limitations that need to be acknowledged. With regard to our experimental protocol, we evaluated a small number of subjects. However, the particular experimental condition utilized offers advantages in terms of reproducibility, magnitudes, and rates of changes in preload. Similarly, invasive hemodynamic measures of filling pressures and relaxation indexes were not performed.

DTE and RT3DE data sets were acquired during different parabolas; as parabolic flights are known to generate repeatable changes in hydrostatic pressure, this has not affected our results. Moreover, after each parabola, the baseline conditions were restored by a 2-min period of steady-state 1 Gz. Even if the images were acquired immediately after the preload change, we cannot exclude that the immediate activation of compensatory mechanisms could have affected our results. Also, abdominal organ pressure on the heart and organ displacement was not measured, and could have affected our results. However, as we performed two-dimensional DTE and three-dimensional ultrasound imaging, we were able to minimize this limitation, following the motion of the heart throughout the parabola. With regard to the imaging methodology, RT3DE is a “near” real-time technique that requires temporal registration of a number of subsegments acquired from four consecutive beats. Accordingly, it was not possible to acquire data sets representative of consecutive cardiac cycles along the whole parabola, but only one data set for each gravity phase. As with any one-dimensional Doppler technique, DTE imaging is angle dependent, and regional velocity estimates can be influenced by overall heart motion, cardiac rotation, and contraction in adjacent segments. To minimize artefacts, we focused our analysis on the basal portion of the interventricular septum, which is known to be less influenced by these factors, having particular care in aligning the ultrasound beam as parallel as possible to the direction of the myocardial septal motion.

With regard to data analysis, the semiautomated segmentation procedure utilized to measure LV volumes requires one to manually initialize the endocardial borders, which is a subjective procedure. Nevertheless, this technique was previously found to be highly reproducible and accurate (4). Also, the analysis of DTE data required manual interaction in the frame-by-frame repositioning of the ROI in correspondence with the segment to be analyzed. However, DTE has been previously shown to be a robust and reproducible technique suitable for clinical application in the quantification of regional myocardial function, and the reported levels of intra- and interobserver variability for DTE-derived parameters are small when compared with the changes we measured in each subject due to changes in gravity (22).

Summary and conclusions. We used parabolic flights and LBNP to rapidly induce changes in loading conditions in normal subjects and to examine the immediate effects on LV basal IVS tissue velocities, strain, and SR measured by DTE. Our results are in agreement with findings previously observed using animal models: S’, E’, and A’ were reduced in the 1.8-Gz, LBNP group.
phase of the parabola, corresponding to a reduction in venous return, while E', A' and PSE were increased during the 0-Gz phase, corresponding to an increase in venous return. By applying a LBNP at ~50 mmHg to reduce venous return during the 0-Gz phase, it was possible to confirm the load dependency of E' and A' velocities, and PSE. Our finding supports the hypothesis that S' SR is a preload-independent index of contractile function, while SR E' and SR A' could reflect more complex interactions between myocardial properties and loading conditions. These facts should be considered in the utilization of DTE in clinical practice. Additional studies are required to assess whether these relationships are altered in clinical disease states.

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