Effect of Large Variations in Preload on Left Ventricular Performance Characteristics in Normal Subjects

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SUMMARY The normal human left ventricular response to large variations in preload was studied in 12 young men. M-mode echocardiograms were recorded at supine rest and compared with studies obtained during head-down tilt (HDT) at 5° and during progressive lower body negative pressure (LBNP) to −40 mm Hg.

During HDT, end-diastolic volume (EDV) increased 23% (p < 0.001), stroke volume (SV) increased 35% (p < 0.001) and ejection fraction (EF) increased 10% (p < 0.05). Heart rate (HR) decreased by 5 beats/min (p < 0.025). During LBNP, EDV decreased 28% (p < 0.001), end-systolic volume (ESV) decreased 21% (p < 0.001) and SV decreased 33% (p < 0.001). LBNP was accompanied by a minor increase in HR (9 beats/min, p < 0.001) and a small increase in systolic blood pressure (11 mm Hg, p < 0.01). Comparisons between measurements obtained during HDT and LBNP showed significant differences in EDV, ESV, SV, EF, HR and diastolic blood pressure. The mean velocity of circumferential fiber shortening was unchanged.

Our data indicate that the mean velocity of circumferential fiber shortening is an index of contractile state that is independent of preload, whereas other echocardiographic measurements are significantly altered by large changes in preload.

THE RESPONSE of the normal human left ventricle to changes in preload has been studied by various methods. However, the range of preload variation has been limited, and the results have often been difficult to interpret due to simultaneous changes in arterial blood pressure and heart rate. Previous studies in our laboratory showed that large variations in preload with minimal effects on heart rate or arterial blood pressure can be induced noninvasively by head-down tilt and lower body negative pressure (LBNP). The primary purpose of the study was to define echocardiographically the extreme ranges of the normal relationship between left ventricular end-diastolic dimensions and stroke volume (i.e., a classic Frank-Starling curve). We also studied the effect of wide variations in preload on commonly used indexes of myocardial contractile state.

Materials and Methods

Twelve normal male volunteers, ages 22–31 years, were studied. Details of the protocol were explained, and each subject gave informed written consent. The study protocol was reviewed and approved by the Human Research Review Committee at the University of Texas Health Science Center at Dallas. The subjects underwent physical examination and were in excellent health. No medications were being taken at the time of the studies.

Echocardiograms were obtained using a Unirad 100 series ultrasonoscope, model 902, with a 2.25-MHz, 13-mm-diameter transducer collimated to 7.5 cm, with a repetition rate of 1000 Hz. M-mode tracings and an ECG were recorded on a Honeywell 1856A strip-chart recorder. All studies were performed with the patient recumbent. The transducer was placed in the third, fourth or fifth intercostal space, depending on the size of the subject. After identification of the characteristic echoes of the mitral leaflets, a sweep was recorded by inferolateral rotation of the transducer, to include echoes from the interventricular septum and posterior left ventricular wall.

Endocardial echoes of the left side of the interventricular septum and the posterior left ventricular wall were identified as suggested by Popp et al. Left ventricular volumes and stroke volumes were calculated according to the method of Teichholz et al. The mean velocity of circumferential fiber shortening (Vcf) was estimated by the method of Cooper and colleagues. Normal Vcf in this laboratory is 0.67–1.59 cm/sec. To determine whether large variations in preload significantly affected the measurement of left ventricular ejection time, supplementary studies were carried out on five different normal subjects. Ejection times were measured by three methods: from a simultaneous carotid pulse tracing, from an aortic root echocardiogram, and from the echocardiogram of the body of the left ventricle, as recommended by Cooper et al. Mean Vcf was estimated during control studies, head-down tilt, and LBNP.
left ventricular echo correlated well with those from carotid pulse tracings \((y = 0.95x + 0.04, r = 0.95, p < 0.001)\). The \(r^2\) was less than 5% (0.05 circ/sec). Similar results were obtained when data from the left ventricular echo were compared with data from the aortic root echo.

Echocardiographic measurements were made separately by two of the investigators, who had no knowledge of the subjects’ circumstances. In each subject, at least three cardiac cycles were analyzed during expiration and the measurements were averaged. Each measurement used was the mean of two observers. When the two series of baseline data were compared to determine reproducibility of echocardiographic measurements, the correlation coefficients were 0.97 (\(r^2 = 0.12\) cm) for end-diastolic dimension and 0.96 (\(r^2 = 0.13\) cm) for end-systolic dimension. Interobserver variability was small; when measurements of end-diastolic dimension were compared, the \(r^2\) of the correlation was 0.06 cm. In a separate series of resting studies of 11 subjects with no maneuvers performed, two serial measurements obtained at least 2 hours apart provided intraobserver variability data and showed correlation coefficients of 0.99 (\(r^2 = 0.07\) cm) for end-diastolic dimension and 0.98 (\(r^2 = 0.10\) cm) for end-systolic dimension.

These data represent an overall intraobserver variability for measurements of left ventricular dimensions of 1.9 ± 0.4%, which compares favorably with data from other laboratories.\(^1\)\(^,\)\(^2\)

The heart rate and Frank lead ECG were continuously monitored and recorded by a Texas Instruments oscillograph. Blood pressure readings were obtained at 1-minute intervals throughout each intervention by programmed electrophygmanometer (Narco Systems, Inc.) and recorded by the same oscillograph. Ahmad et al.\(^3\) found good agreement between these measurements and auscultatory readings. Mean arterial pressure was calculated as diastolic pressure plus one-third of the pulse pressure.

All studies were performed with the patient in the supine position at the same time of day according to the following protocol: (1) Baseline studies were carried out after a rest period of 15 minutes. (2) An increase in preload was produced by 5° of head-down tilt. Data were recorded after 90 minutes of tilt, the time of maximal effect of this intervention on the dimensional measurements of the left ventricle according to studies in our laboratory.\(^3\) Head-down tilt at this angle produces a transient increase in central venous pressure of about 2.5 cm of water, with a return to baseline when the left ventricle reaches its maximal size. (3) Baseline studies were repeated after a rest period of 15 minutes. (4) A decrease in preload was induced by a gradual application of LBNP to -40 mm Hg; pressure was lowered in increments of -8, -16, and -32 to -40 mm Hg at intervals of 1.3 and 3 minutes, respectively. Data were recorded during the last 15 seconds of the 5-minute application of LBNP at -40 mm Hg. The LBNP protocol and the device have been described in detail.\(^5\)\(^,\)\(^6\)\(^,\)\(^9\) LBNP of this magnitude produces venous pooling with a progressive increase in leg volume of 500–700 ml and a similar or slightly larger reduction in circulating blood volume. Central venous pressure decreases by approximately 5 cm of water. The order of procedures 2 and 4 was randomly allocated.

Data obtained before and during each intervention were compared and significant differences determined by analysis of variance for single-factor experiments having repeated measures.\(^21\) When significant differences (\(p < 0.05\)) between groups were found, within-group differences were determined by the Student-Newman-Keuls multiple-range test, and values < 0.05 were considered significant. The interrelationships between several measurements were also analyzed by linear regression.

**Results**

The changes in left ventricular volumes, ejection fraction, mean Vcf, heart rate and blood pressure are summarized in table 1. There were no significant differences between control data obtained before head-down tilt and before LBNP. Analysis of variance demonstrated significant changes during the interventions in all variables except mean Vcf and blood pressure.

The changes in heart rate and systolic blood pressure were small relative to the changes in stroke volume. Therefore, cardiac output was proportional to stroke volume and inversely proportional to systemic resistance. Mean systemic peripheral resistance, estimated as the ratio of mean arterial pressure (mm Hg) to cardiac output (l/min) (derived from the product of echocardiographic stroke volume and heart rate), was 16 units during head-down tilt and 27 units during LBNP.

During head-down tilt, mean end-diastolic volume increased 23%, from 110 ± 9 ml to 134 ± 10 ml (\(p < 0.001\)), mean stroke volume increased 35%, from 67 ± 6 ml to 86 ± 6 ml (\(p < 0.001\)) and mean ejection fraction increased from 60 ± 2% to 66 ± 2% (\(p < 0.05\)) (fig. 1). Mean end-diastolic diameter increased from 4.8 ± 0.2 cm to 5.2 ± 0.2 cm and mean end-systolic diameter from 3.2 ± 0.1 cm to 3.3 ± 0.1 cm. Concomitantly, the mean heart rate decreased from 61 ± 2 to 56 ± 3 beats/min (\(p < 0.025\)) (fig. 2). End-systolic volume, mean Vcf and blood pressure did not change significantly during head-down tilt (figs. 1 and 2).

During LBNP, mean end-diastolic volume decreased 28%, from 111 ± 8 ml to 82 ± 9 ml (\(p < 0.001\)), mean end-systolic volume decreased 21%, from 46 ± 5 ml to 36 ± 5 ml (\(p < 0.001\)), and mean stroke volume decreased 33%, from 65 ± 4 ml to 45 ± 5 ml (\(p < 0.001\)) (fig. 1). Mean end-diastolic diameter decreased from 4.8 ± 0.2 cm to 4.2 ± 0.2 cm and mean end-systolic diameter from 3.3 ± 0.1 cm to 3.0 ± 0.2 cm. Concomitantly, heart rate increased from 57 ± 2 to 66 ± 3 beats/min (\(p < 0.001\)) and systolic blood pressure decreased from 116 ± 4 mm Hg to 105 ± 4 mm Hg (\(p < 0.01\)) (fig. 2). Ejection fraction, mean Vcf and mean or diastolic blood pressures did not change during LBNP (figs. 1 and 2).
Table 1. Effects of Head-down Tilt and Lower Body Negative Pressure on Left Ventricular Dimensions, Heart Rate and Blood Pressure

<table>
<thead>
<tr>
<th>Head-down tilt</th>
<th>Lower body negative pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (C)</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>110 ± 9</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>44 ± 5</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>67 ± 6</td>
</tr>
<tr>
<td>EF (%)</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Mean Vcf (circ/sec)</td>
<td>0.85 ± 0.06</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>61 ± 2</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>82 ± 3</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>116 ± 4</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>65 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Abbreviations: C = control; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; Vcf = velocity of circumferential fiber shortening; HR = heart rate; BP = arterial blood pressure; LBNP = lower body negative pressure.

When mean values obtained during head-down tilt and LBNP were compared, there were significant differences in end-diastolic volume (p < 0.001), end-systolic volume (p < 0.001), stroke volume (p < 0.001), ejection fraction (p < 0.005), heart rate (p < 0.001) and diastolic blood pressure (p < 0.005). No differences existed in values for mean Vcf and mean or systolic blood pressures.

Individual data relating stroke volume (SV) to end-diastolic volume (EDV) at rest and during both interventions are shown in figure 3. The data conform to a normal left ventricular function curve, best described by the experimental function $SV = 0.36 EDV^{1.1}$ ml ($r = 0.93$, $p < 0.001$), but not significantly different from the linear regression $SV = 0.6 EDV + 0.57$ ($r = 0.92$, $p < 0.001$). The SEE of the linear regression was 9 ml, and the SEM of the intercept was 4 ml and of the slope 0.04. The intercept was not significantly different from zero. Therefore, the slope is the equivalent of the ejection fraction over the range of end-diastolic volumes studied, implying that the induced variations in preload were not sufficient to produce a plateau phase of the Frank-Starling curve.

Table 2 lists the correlation coefficients of linear progression obtained when percent changes from control for each measurement during each intervention were compared. In addition to the correlation with changes in stroke volume, changes in end-diastolic volume positively correlated with changes in end-systolic volume and ejection fraction. Changes in end-systolic volume also correlated positively with changes in stroke volume and systolic blood pressure. A positive correlation existed between changes in stroke volume and ejection fraction. Although mean Vcf changes did not correlate significantly with changes in end-diastolic, end-systolic and stroke volumes, a positive correlation existed with changes in ejection fraction. Changes in end-diastolic, end-systolic and stroke volumes correlated negatively with heart rate changes.

Discussion

This study shows that in normal human subjects, wide variations in preload and end-diastolic volume produce remarkably predictable changes in stroke volume that conform to the normal ascending Frank-Starling curve. Unexpectedly, end-systolic and end-diastolic volumes correlated positively.
Studies in humans and experimental animals have generally also shown a linear relationship between left ventricular end-diastolic volume, similar to our data in figure 3.22-28 The relationship between left ventricular stroke volume and end-diastolic pressure has also usually been found to be approximately linear within the normal pressure range. However, Parker and Case24 suggested that the normal human left ventricle operates near its maximal volume in the supine position. They summarized several of their human series studied during various interventions with changes in blood volume and filling pressures and concluded that the human left ventricular function curve, using stroke work index and stroke volume index as a function of end-diastolic pressure, reaches a plateau at an end-diastolic pressure level of about 20 mm Hg in the supine position and that the left ventricular pressure-volume curve shows little change in volume for any pressure increment above 10 mm Hg.

Our findings do not support this concept. The change of position from supine to head-down tilt at 5° produced a large increase in end-diastolic volume and stroke volume. Left ventricular end-diastolic pressures were not measured, but our previous studies in normal young males indicate that tilt produces only a modest and transient elevation of the central venous pressure preceding the increase in left ventricular volume.13-20 The average increase in 10 subjects was 2.5 cm water.20 Changes in central venous pressure do not necessarily parallel changes in left ventricular end-diastolic pressure, but it seems highly unlikely that changes in left ventricular end-diastolic pressure would be of a different order of magnitude from the right-sided pressures. The central venous pressure changes during LBNP, according to the technique used in our laboratory, tend to be slightly larger than during tilt (5 cm water compared with 2.5 cm water), but the changes in left ventricular end-diastolic volume and stroke volume are similar during both interventions. The systemic hemodynamic changes during LBNP in the present series were comparable to those reported by others during LBNP and head-up tilt.3,6,10,24 LBNP at levels of -40 to -50 mm Hg produces an acute decrease in circulating blood volume by 500-1000 ml by venous pooling in the legs.3-8 The central fluid shift during head-down tilt is more difficult to quantify, but comparisons with central venous pressure measurements during acute i.v. infusion of dextran or saline suggest that head-down tilt at 5° is the equivalent of an acute blood volume increase of about 500 ml.7

The range of left ventricular volume changes in our series is larger than that in previous studies,2,5,6,10 except for the series presented by Parker and Case,24 which comprised several subgroups. The extended preload range made it possible to examine in detail the relation between preload and commonly used measures of left ventricular performance — ejection fraction, mean Vcf, and end-systolic volume — taking into account the uncertainties inherent in the analysis of the intrinsic contractile state of the human heart.

There is an apparent contradiction in our results on ejection fraction, i.e., the relationship between end-diastolic volume and stroke volume. The data in figure 3 show a linear correlation with an intercept that is not significantly different from zero. This implies that the

| Table 2. Linear Correlation Coefficients (r) Between Changes in Blood Pressures, Heart Rate and Left Ventricular Performance Characteristics |
|-----------------|-----------------|-----------------|-----------------|
| ΔEDV            | ΔESV            | ΔSV             | ΔEF             | ΔHR             |
| ΔESV            | 0.78*           | 0.94*           | 0.55*           | -0.68*          |
| ΔSV             | -0.04           | 0.72*           | -0.94*          | -0.70           |
| ΔEF             | -0.04           | 0.60*           | -0.35           | -0.18           |
| ΔMean Vcf       | 0.33            | 0.05            | 0.39            | 0.02            |
| ΔMean BP        | 0.06            | 0.32            | -0.35           | -0.36           |
| ΔSystolic BP    | 0.36            | 0.52*           | -0.14           | -0.36           |
| ΔDiastolic BP   | -0.17           | -0.01           | -0.19           | -0.35           | 0.05 |

Individual data during head-down tilt and lower body negative pressure normalized and expressed as percentages of control measurements obtained at supine rest.

*When r = 0.40, p < 0.05.
Abbreviations: See table 1.
normal human left ventricular ejection fraction is constant and independent of end-diastolic volume. However, a significant preload effect on the ejection fraction became apparent (fig. 1, table 2) when the effect of baseline interindividual variations with respect to end-diastolic volume was eliminated and the analysis was limited to interindividual variations induced by LBNP and head-down tilt. The ejection fraction was significantly lower during LBNP at a reduced end-diastolic volume. During this intervention, there was a small but significant increase in heart rate and a decrease in systolic blood pressure, i.e., changes that would have been expected to increase ejection fraction. The positive correlation between end-diastolic volume and ejection fraction is in agreement with data obtained during acute interventions.22, 26

Mean Vcf is the most widely accepted clinical echocardiographic measurement of contractile state.27, 28 Our data confirm that preload has an appreciable effect on the mean Vcf. Heart rate and blood pressure changes during tilt and LBNP were small and would not by themselves affect the Vcf. Studies in normal subjects have shown that mean Vcf is insensitive to changes in preload, and large acute alterations in heart rate and blood pressure do change mean Vcf.5, 10, 13, 29 An atropine-induced increase in heart rate averaging 34 beats/min produced an increase in mean Vcf of 13% in human subjects, and a phenolamine-induced mean increase in systolic blood pressure of 38 mm Hg reduced mean Vcf by 21%.27

End-systolic volume is useful in differentiating changes in left ventricular contractility from changes induced by the Frank-Starling mechanism.22, 26, 30 In angiographic human studies in which left ventricular dimensions were measured, an acute increase in preload by contrast injection produced a 31% change in end-diastolic dimensions without a significant change in end-systolic dimensions.31 If the alterations in preload induced by the interventions of head-down tilt to 5° and LBNP to -40 mm Hg were pure volume interventions, one would anticipate minimal or no change in end-systolic volume during these interventions; however, our data (table 2) showed a strong positive correlation between end-systolic and end-diastolic volumes. Studies in our laboratory with unidirectional changes in ventricular filling have shown a similar but nonsignificant trend in smaller groups.12, 13 Further, changes in diastolic blood pressure can be associated with alterations in end-systolic pressure relative to peak systolic pressure. This is an alternative explanation for the higher end-systolic volume and lower ejection fraction during tilt than during LBNP. Grossman et al.30 showed that acute changes in end-systolic volume can occur without changes in end-systolic pressure. In the presence of such large changes in ventricular volumes, systolic blood pressure could be an inaccurate index of wall stress.32 The decreased end-systolic volume during LBNP might reflect a decrease in afterload that is relatively larger than the decrease in preload.

Our findings are nevertheless difficult to explain, particularly because ejection fraction showed variations in the opposite direction and mean Vcf remained constant throughout the study. Also, large acute changes in end-diastolic volume might have significant effects on end-systolic volume unrelated to changes in contractile state. A more likely explanation is inherent in the method of estimating left ventricular volumes from the echocardiographic measurements.15 The calculation of ventricular volume is based on the assumption that the left ventricle is always ellipsoidal and the minor diameter is always half of the major diameter.16 It is possible that at the extremes of ventricular volumes in our subjects, the left ventricle altered its shape, becoming more cylindrical at small volumes and more globular at higher volumes. The regression equation of Teichholz et al.14 was derived from a series of angiographically normal ventricles over a wider range of volumes than those in our subjects during the interventions. However, acute changes in left ventricular end-diastolic volume might well be associated with significant variations in shape, whereas the normal ventricle at rest, irrespective of size, might conform to the configuration implicit in

![Figure 3. Relationship between left ventricular end-diastolic and stroke volumes at supine rest (CONTROL) during head-down tilt (TILT) and during lower body negative pressure (LBNP).](image-url)
the standard formula for estimation of volumes. Two-dimensional echocardiographic techniques might be more suitable for assessing possible changes in ventricular shape. Estimations of ventricular volumes by this technique have shown a reasonable correlation with cineangiography.37-38

Thus, our data provide indirect support for the clinical use of mean Vcf as an index of contractile state. Ejection fraction is significantly affected by preload changes. Additional studies are necessary to determine the relationship between preload and left ventricular end-systolic volume as determined by standard echocardiographic techniques.

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