Alterations in Preload and Ejection Phase Indices of Left Ventricular Performance

By Larry S. Rankin, M.D., Sally Moos, and William Grossman, M.D.

SUMMARY

Ejection phase indices such as mean velocity of circumferential fiber shortening (Ve), ejection fraction (EF), and mean normalized systolic ejection rate (MSER) are thought to reflect the level of left ventricular (LV) inotropic state. Although known to be influenced by changes in afterload, their response to altered preload is less certain. This question was examined in ten normal subjects studied in the supine position and after 10 min of 75° head-up tilt. Echo LV diameter (D) and carotid pulse recordings were used to calculate LV ejection time, Ve, MSER, LV end-diastolic and stroke volumes (EDV and SV, by DP formula), and ejection fraction. Systemic blood pressure (BP) was measured by cuff, and heart rate (HR) counted from the ECG. Calculated LVEDV decreased with tilt (115 ± 8 vs 82 ± 7 ml, P < 0.001), as did SV (81 ± 6 to 54 ± 6 ml, P < 0.001), and ejection time (0.31 ± 0.01 to 0.27 ± 0.00 sec, P < 0.001), but there was no significant change in systolic or diastolic BP or HR. Ve, EF, and MSER were not significantly altered by tilt (1.09 ± 0.04 to 1.12 ± 0.05 circ/sec; 0.70 ± 0.02 to 0.65 ± 0.02; and 2.29 ± 0.07 to 2.43 ± 0.08 end-diastolic volumes/sec, respectively). Ve, MSER, and EF appear relatively unaffected by acute alterations in preload. That compensatory sympathetic responses blunted potential changes cannot be excluded, although HR was not found to have increased.

Additional Indexing Words:

Echocardiography Velocity of circumferential fiber shortening Tilt
Myocardial mechanics Myocardial contractility

THE VIGOR OF LEFT VENTRICULAR CONTRACTION is determined by the interaction of a number of physiologic variables. Chief among these are the load and fiber length immediately prior to contraction (preload), the load during contraction (afterload), and the intensity of the active state (myocardial "contractility," "inotropy"). Preload and afterload of the human left ventricle can be estimated with reasonable accuracy, but measurement of myocardial contractility has proved elusive.

In recent reports on this subject,2,3 it has been pointed out that contractility indices derived from analysis of left ventricular ejection performance appear more promising than those derived from analysis of isovolumic contraction. While previous work4,5 has shown that such ejection phase indices as velocity of circumferential fiber shortening and ejection fraction are influenced by left ventricular afterload as well as contractile state, the degree to which these indices are independent of alteration in resting fiber length remains a matter of controversy.6,9 Clarification in normal hearts of the specificity of these contractility indices is important if they are to be utilized with understanding in the evaluation of patients with heart disease.

This paper reports the use of head-up tilt and the resultant changes in left ventricular volume to study the degree to which left ventricular ejection phase indices are altered by change in preload. We employed noninvasive techniques to study normal volunteers, and assessed three ejection phase indices in particular: mean velocity of circumferential fiber shortening (Ve), mean normalized systolic ejection rate, and left ventricular ejection fraction. The results suggest that when afterload is constant, acute changes in preload do not substantially affect these indices, thus supporting their use in the assessment of left ventricular inotropic state.

Methods

The study subjects were ten normal volunteers, seven men and three women, between the ages of 20 and 35 years. A strip chart echocardiogram was recorded with a Smith-Kline Ekoline 20A Ultrasonoscope interfaced with either a Cambridge Multiple Channel Physiologic Recorder or an Electronics for Medicine DR-12 recorder. Aerotech ultrasonic 2.25 MHz transducers were utilized, emitting 1000 pulses/sec, with a one-half inch diameter face and 7.5 cm internal focus. Lead II of the electrocardiogram was recorded simultaneously with the echocardiogram, as was a
carotid pulse tracing utilizing a Hellige external pulse
transducer. Blood pressure was measured by sphyg-
monanometry at the beginning and end of each data
collection period.

Control data were obtained with the subject lying on a tilt
table in the supine position for at least ten minutes
equilibration. Tilt data were then recorded after ten minutes
of 75° head-up tilt.

An echocardiographic volume study was recorded by the
method of Feigenbaum,10 utilizing the scanning technique
to carefully define the endocardium and left ventricular side
of the septum. Care was taken to obtain left ventricular in-
ternal dimensions from a point just below the mitral leaflets
at the level of the chordae tendineae. Particular attention
was paid to maintaining this location of the echo beam in
each subject when tilting from the supine to upright posi-
tion. The left ventricular end-diastolic diameter (LVEDD)
was measured at the peak of the R wave of the ECG, and
the left ventricular end-systolic diameter (LVESD) was
measured at the point of maximum inward movement of the
left ventricular posterior wall (fig. 1). Left ventricular end-
diastolic (LVEDV) and end-systolic (LVESV) volumes were
calculated by the D4 formula,10 left ventricular stroke
volume (SV) was calculated as LVEDV − LVESV, and ejec-
tion fraction (EF) was determined as SV/LVEDV. Left ven-
tricular ejection time (LVET) was measured directly from
the carotid pulse tracing, and heart rate was calculated from
the electrocardiogram. LVEDV was used as an approxima-
tion of left ventricular preload, while diastolic blood
pressure was considered an estimate of left ventricular
afterload. Ventricular preload is more specifically defined as
wall stress at end-diastole which includes end-diastolic
pressure and wall thickness as well as volume. Volume,
however, is a major contributor to wall stress and should
accurately reflect preload, particularly in the acute situation.
The possible errors introduced by these approximations are
commented upon in the Discussion section.

Mean velocity of circumferential fiber shortening (V_{cf})
was calculated from the formula
\[ V_{cf} = \frac{(LVEDD - LVESD)/(LVEDD)/(LVET) }{ } \]
and expressed in circum-
ferences/second.2 Mean normalized systolic ejection rate
(MSER) was calculated by the method of Karliner et al.2 as:
\[ MSER = \frac{(LVEDV - LVESV)/(LVEDV)/(LVET) }{ } \]
and expressed as end-diastolic volumes/sec. All data represent
an average of six to eight beats from each subject in both the
supine and tilt positions. Four subjects were studied on
repeated occasions and the echocardiographic mea-
surements and derived data were found to be entirely
reproducible and consistent. Control values were compared
for each subject with values during tilt, and results are ex-
pressed statistically in terms of standard error of the mean
and Student’s paired t-test, using P < 0.01 as statistically
significant.

Results

Tilting resulted in a significant decrease in left
ventricular preload (LVEDV), as seen in table 1 and
illustrated in figures 2 and 3. Calculated LVEDV
decreased from 115 ± 8 ml to 82 ± 7 ml (P < 0.001)
with tilting. However, this maneuver did not alter
blood pressure or heart rate significantly (table 1):
diastolic blood pressure remained unchanged (77 ± 2
mm Hg to 79 ± 2 mm Hg) from control, as did heart
rate (63 ± 2 to 66 ± 4 beats/min).

Accompanying the preload decline induced by
tilting, SV decreased significantly (81 ± 6 ml to
54 ± 6 ml, P < 0.001). A significant decrease also oc-
curred in left ventricular ejection time (0.31 ± 0.01
sec to 0.27 sec, P < 0.001).

Despite the consistent decline in preload, ejection
phase indices of left ventricular performance showed
variable changes and were unaltered for the group as
a whole as illustrated in figure 4. V_{cf} showed a slight
increase (1.09 ± 0.04 circ/sec to 1.12 ± 0.05 circ/sec,
NS) as did MSER (2.29 ± 0.07 to 2.43 ± 0.08 end-
diastolic volumes/sec, NS) while EF showed a small
decrease (0.70 ± 0.02 to 0.65 ± 0.02, NS).

Discussion

The transformation of chemical into mechanical
energy by cardiac muscle manifests itself as tension
development and fiber shortening. Both can be
studied in terms of rate and magnitude parameters,
and the vigor and efficiency of the muscle may be
assessed by consideration of these measurements. In
the intact left ventricle such assessment is more
difficult, but attempts have been made by examining
the rate and magnitude of wall tension development,
as well as the velocity and extent of fiber shortening.
Since fiber shortening is essentially limited to the eje-
cution phase of left ventricular contraction, measure-
ments related to left ventricular fiber shorten-
ing have been termed ejection phase indices of
myocardial function.

In utilizing any index of myocardial function, it is
important to understand the expected physiologic
Table 1

Altered Preload and Left Ventricular Ejection Phase Indices

<table>
<thead>
<tr>
<th>Subject</th>
<th>LVEDV (cc)</th>
<th>LVESV (cc)</th>
<th>SV (cc)</th>
<th>HR (beats/min)</th>
<th>BP (mm Hg)</th>
<th>LVET (sec)</th>
<th>Vcf (circ/sec)</th>
<th>EF</th>
<th>MSER (EDV/sec)</th>
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<tr>
<td>1 c</td>
<td>118</td>
<td>43</td>
<td>75</td>
<td>71</td>
<td>112/70</td>
<td>0.31</td>
<td>0.92</td>
<td>0.64</td>
<td>2.05</td>
</tr>
<tr>
<td>T</td>
<td>85</td>
<td>22</td>
<td>63</td>
<td>71</td>
<td>110/76</td>
<td>0.28</td>
<td>1.30</td>
<td>0.74</td>
<td>2.65</td>
</tr>
<tr>
<td>2 c</td>
<td>125</td>
<td>33</td>
<td>92</td>
<td>71</td>
<td>104/70</td>
<td>0.30</td>
<td>1.20</td>
<td>0.74</td>
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<td>22</td>
<td>42</td>
<td>86</td>
<td>104/70</td>
<td>0.28</td>
<td>1.07</td>
<td>0.66</td>
<td>2.34</td>
</tr>
<tr>
<td>3 c</td>
<td>80</td>
<td>27</td>
<td>53</td>
<td>54</td>
<td>108/70</td>
<td>0.35</td>
<td>0.86</td>
<td>0.66</td>
<td>1.89</td>
</tr>
<tr>
<td>T</td>
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<td>27</td>
<td>37</td>
<td>48</td>
<td>108/70</td>
<td>0.28</td>
<td>0.89</td>
<td>0.58</td>
<td>2.06</td>
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<tr>
<td>4 c</td>
<td>97</td>
<td>20</td>
<td>78</td>
<td>63</td>
<td>128/78</td>
<td>0.32</td>
<td>1.29</td>
<td>0.80</td>
<td>2.49</td>
</tr>
<tr>
<td>T</td>
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<td>30</td>
<td>55</td>
<td>66</td>
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<td>0.27</td>
<td>1.09</td>
<td>0.65</td>
<td>2.41</td>
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<tr>
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<td>71</td>
<td>68</td>
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<td>0.28</td>
<td>1.14</td>
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<td>2.45</td>
</tr>
<tr>
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<td>39</td>
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<td>0.57</td>
<td>2.10</td>
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<tr>
<td>6 c</td>
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<td>66</td>
<td>130/90</td>
<td>0.26</td>
<td>1.41</td>
<td>0.75</td>
<td>2.89</td>
</tr>
<tr>
<td>7 c</td>
<td>118</td>
<td>30</td>
<td>88</td>
<td>53</td>
<td>128/78</td>
<td>0.32</td>
<td>1.15</td>
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<tr>
<td>T</td>
<td>111</td>
<td>30</td>
<td>81</td>
<td>54</td>
<td>128/76</td>
<td>0.28</td>
<td>1.26</td>
<td>0.73</td>
<td>2.61</td>
</tr>
<tr>
<td>8 c</td>
<td>133</td>
<td>43</td>
<td>90</td>
<td>68</td>
<td>110/85</td>
<td>0.27</td>
<td>1.16</td>
<td>0.68</td>
<td>2.51</td>
</tr>
<tr>
<td>T</td>
<td>85</td>
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<td>52</td>
<td>79</td>
<td>112/85</td>
<td>0.24</td>
<td>1.14</td>
<td>0.62</td>
<td>2.56</td>
</tr>
<tr>
<td>9 c</td>
<td>158</td>
<td>51</td>
<td>107</td>
<td>54</td>
<td>108/75</td>
<td>0.32</td>
<td>0.98</td>
<td>0.68</td>
<td>2.12</td>
</tr>
<tr>
<td>T</td>
<td>91</td>
<td>39</td>
<td>52</td>
<td>60</td>
<td>110/80</td>
<td>0.26</td>
<td>0.94</td>
<td>0.57</td>
<td>2.19</td>
</tr>
<tr>
<td>10 c</td>
<td>80</td>
<td>24</td>
<td>55</td>
<td>68</td>
<td>110/80</td>
<td>0.31</td>
<td>1.05</td>
<td>0.69</td>
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</tr>
<tr>
<td>T</td>
<td>47</td>
<td>16</td>
<td>31</td>
<td>73</td>
<td>120/80</td>
<td>0.26</td>
<td>1.17</td>
<td>0.66</td>
<td>2.55</td>
</tr>
</tbody>
</table>

Mean ± SEM: c 115 ± 8 34 ± 3 81 ± 6 63 ± 2 114 ± 3/77 ± 2 0.31 ± 0.01 1.09 ± 0.04 0.70 ± 0.02 2.29 ± 0.07
T 82 ± 7 28 ± 2 54 ± 6 66 ± 4 116 ± 3/79 ± 2 0.27 ± .00 1.12 ± 0.05 0.65 ± 0.02 2.43 ± 0.08

P value <0.001 NS <0.001 NS NS <.001 NS NS

Abbreviations: LVEDV and LVESV = left ventricular end diastolic and end systolic volumes; SV = stroke volume; HR = heart rate; BP = blood pressure; LVET = left ventricular ejection time; Vcf = mean velocity of circumferential fiber shortening; EF = ejection fraction; MSER = mean systolic ejection rate; SEM = standard error of the mean; NS = not significant.
**Figure 2**

LV volume echocardiogram, carotid pulse tracing, and ECG in a normal subject supine (left), and after 10 min of 75° head-up tilt (right). Interventricular septum and posterior wall (PW) endocardium and epicardium are well visualised. Tilt was associated with a substantial decline in end-diastolic diameter, used as a measure of LV preload. Ejection time, measured from the carotid tracing, also declined.

**Figure 3**

Left ventricular end-diastolic diameter measurements in the supine position (control) and after 10 min of 75° head-up tilt. Measurements for each patient are represented as a pair of points connected by a straight line. Mean values are represented by the horizontal bars. As can be seen, left ventricular end-diastolic diameter decreased in all patients with head-up tilt, suggesting a decline in preload.

**Figure 4**

Effects of head-up tilt on mean velocity of circumferential fiber shortening ($V_{CF}$), mean systolic ejection rate (MSER) and ejection fraction (EF). Despite the appreciable decline in preload, no significant changes occurred in these ejection phase indices of left ventricular performance. Average values for the control (C) and tilt (T) measurements are given by the cross-hatched and clear bars, respectively. Brackets represent standard errors of the mean.
fluctuation of that index in the normal heart. With regard to ejection phase indices, changes in left ventricular afterload appear to be important determinants of these physiologic fluctuations. Ross and co-workers and Urschel et al. have shown that LV circumferential fiber shortening rate and ejection fraction are both depressed when afterload is suddenly increased in the anesthetized open-chest dog. Covell and his colleagues have shown that mean V$_{ef}$ is inversely proportional to changes in left ventricular afterload induced by phenylephrine infusion in normal conscious dogs. It might be expected that similar afterload dependence should be seen with normalized LV ejection rate as well, but to our knowledge this question has not been specifically examined.

The relation between left ventricular ejection phase indices and altered preload is unclear. Covell et al. produced acute increases in preload by volume expansion in dogs and found no significant change in V$_{ef}$. In another recent report, Benzing et al. found a variable correlation between preload and V$_{ef}$, although for the entire group of experimental animals there was no significant change. In contrast, in the analysis of atrial fibrillation, there was a direct correlation between V$_{ef}$ and preload which was of greater importance than either afterload or the ratio of the two preceding R-R intervals. The atrial fibrillation model is complex, however, and extrapolation to patients with normal sinus rhythm is uncertain. Krayenbühl et al. produced preload changes in anesthetized dogs by transfusion, and noted an increase in LV ejection fraction from 37% to 42% at a time when LV end-diastolic pressure increased from 2.2 to 8.5 mm Hg. Although this change in ejection fraction was statistically significant, its physiologic importance is uncertain because of its small size. A somewhat different result was found by Holt who measured LV end-diastolic, end-systolic, and stroke volumes in dogs during plethora and hemorrhage. He found a linear relation between LV stroke volume and end-diastolic volume (EDV) with a slope of .38 (SV/EDV) throughout the range of EDV from 20-55 cc. Thus, in his experiments the stroke volume was a constant function of the end-diastolic volume, suggesting that ejection fraction is uninfluenced by acute preload change.

In our study preload decrease by head-up tilt as approximated by LVEDV decrease was accomplished without change in afterload as defined by diastolic blood pressure. Although the intervention was "acute," measurements were made after 10 min at a point when a steady state appeared to have been reached. In this setting, altered resting fiber length did not change myocardial performance as defined by V$_{ef}$, MSER, or EF. Investigators have demonstrated that maneuvers such as isoproterenol infusion which exert positive inotropic effects on the heart do increase V$_{ef}$, and that ejection phase indices are sensitive in the detection of depressed myocardial function in patients with LV dysfunction. Taken together, these data support the contention that ejection phase indices reflect the inotropic state of the myocardium and are relatively independent of the Frank-Starling mechanism.

Certain important criticisms and shortcomings of this study must be pointed out. First neither preload nor afterload were precisely characterized, but rather estimated from measurements of ventricular chamber size and blood pressure. Preload and afterload are more exactly defined as the wall stresses before and during ventricular contraction. To compute such stresses, a knowledge of simultaneous ventricular pressure, wall thickness and geometry is required, and to obtain such information would require invasive techniques, inappropriate in the study of normal volunteers. In our study, decreases in left ventricular diameter associated with head-up tilt were taken to indicate decreased left ventricular fiber stretch and preload, resulting from a shift in blood away from the central pool. LV internal diameter and calculated volume at end-diastole are major components of wall stress at that time in the cardiac cycle. Correspondingly, use of these parameters should accurately reflect changes in preload. Since after 10 min aortic systolic and diastolic pressures (as estimated by sphygmanomanometry) showed virtually no change compared to pre-tilt control values, we feel it is reasonable to conclude that no major change in afterload had occurred as a result of the tilt. Actually the decrease in chamber diameter at constant aortic pressure suggests a small decline in wall tension, but without knowledge of accompanying changes in wall thickness and chamber geometry, actual afterload cannot be calculated.

A second criticism of this study is that autonomic reflex regulation may have occurred and masked significant changes in the ejection phase indices. Thus, a decrease in ejection phase indices might have been blunted in this study by a compensatory sympathetic response to head-up tilt in these normal volunteers. One would predict, however, that increased sympathetic tone would have likewise produced an increase in heart rate and no such change was demonstrated. Although not measured in this study, peripheral vascular resistance must have increased because of a constant blood pressure but decline in cardiac output (product of heart rate and stroke volume, table 1) produced by tilt. If peripheral vascular resistance were utilized as an indicator of afterload as advocated by some investigators, we
would have predicted a fall in $V_{ef}$ rather than the insignificant increase reported here.

A third criticism of this study is that head-up tilt may have altered the position of the heart in the chest and thereby affected the comparability of the echocardiographic left ventricular diameter measurements. Such a possibility cannot be totally excluded, although every effort was made to ensure comparability of the control and tilt echoes by utilization of the scanning technique, and insisting on identification of the same landmarks (e.g., mitral valve leaflet) in both records. This was felt to be quite important, since echocardiographic studies taken toward the apex of the left ventricle would give falsely low diameter measurements and volume calculations.

In the context of these limitations, this study supports the findings of Covell et al. and extends them to normal human subjects. Further, in this study ejection fraction and mean normalized systolic ejection rate were also examined, and appear similarly unaffected by preload shifts.

It should be emphasized that we have not examined the sensitivity of ejection phase indices to changes in left ventricular inotropic state, nor have we assessed their clinical usefulness. However, recent reports by Karliner et al. and by Peterson and co-workers suggest that these indices have both physiologic sensitivity and clinical usefulness. Ejection phase indices have a major advantage over isovolumic indices of myocardial function in that recent studies have shown that they can be noninvasively measured by ultrasonic techniques, and that these measurements exhibit a high degree of accuracy when referenced against angiographic methods as a standard.

While the effects of acute alterations in preload and afterload are relatively easy to study, the effects of chronic preload and afterload changes are more difficult to assess. Ross and McCullagha showed that circumferential fiber shortening rate was unimpaired in dogs with surgically induced chronic volume overload, as long as myocardial failure was absent. In chronic severe mitral regurgitation, however, fiber shortening rate was reduced, suggesting impaired myocardial function per unit of circumference. The effects of chronic afterload changes on ejection phase indices have not been reported.

Finally, it should be pointed out that $V_{ef}$ and MSER appear to be more sensitive indices of left ventricular performance than EF. This may be due to a summation of effects, since $V_{ef}$ and MSER reflect changes in both extent of shortening and duration of ejection, while EF reflects only extent of shortening.

Improved understanding of the physiologic significance of easily measured indices of myocardial performance such as $V_{ef}$, EF and MSER and their response in normal subjects to maneuvers such as altered body posture should provide the clinician with readily applied investigative tools for the initial and longitudinal evaluation of patients with diseased hearts.

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**References**

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