The Linearity of the End-systolic Pressure-Volume Relationship in Man and Its Sensitivity for Assessment of Left Ventricular Function

Helmuth C. Mehmel, M.D., Benjamin Stockins, M.D., Kai Ruffmann, M.D., Klaus v. Olshausen, M.D., Gerhard Schuler, M.D., and Wolfgang Kübler, M.D.

SUMMARY The linearity and sensitivity of the end-systolic pressure-volume (P-Ves) relation to the inotropic state of the left ventricle were investigated in 11 patients with coronary heart disease and one patient with congestive cardiomyopathy. To minimize autonomic reflex responses, propranolol, 0.15 mg/kg, and atropine, 1 mg, were administered i.v. at the beginning of the study. Three ventriculograms were performed: at rest, after oral isosorbide dinitrate, 10 mg (systolic pressure decrease \( \geq 15 \) mm Hg), and during infusion of methoxamine, 2 mg/min (systolic pressure increase \( \geq 10 \) mm Hg).

The three points of the P-Ves relation showed linearity \((r \geq 0.96)\). The relation between the slope \( k \) of the P-Ves relation and the left ventricular ejection fraction at rest was best described by an exponential function \((r = 0.94)\). The use of peak systolic pressure instead of end-systolic pressure showed equally good results. The intercept of the P-Ves line on the abscissa, which represents the theoretical end-systolic volume at zero pressure, was not related to the ejection fraction under control conditions. The P-Ves relation in postextrasystolic beats was displaced toward the left (smaller end-systolic volumes) and became steeper.

MYOCARDIAL fiber shortening is determined by preload, afterload and contractility, and end-systolic fiber length is inversely proportional to afterload. In the isolated left ventricle, end-systolic fiber length is linearly related to end-systolic tension. In the experimental animal, the isolated left ventricle also shows a linear end-systolic pressure-volume (P-Ves) relationship that is not dependent on preload. The slope of the P-Ves relation is determined by the contractile state and is increased by positive inotropic interventions. Although the concept of the P-Ves relation has been applied for some time in animal experiments, only recently has the P-Ves relation been investigated as a means of assessing left ventricular function in man.

Our study was undertaken to determine (1) whether the P-Ves relation in man is linear; (2) the correlation between the slope \( k \) of the P-Ves relation and other variables of left ventricular function; (3) whether the theoretical volume at zero pressure \( (V_0) \), i.e., the intercept of the P-Ves relation on the abscissa, reliably separates impaired from normal left ventricular function; and (4) whether the end-systolic left ventricular pressure can be replaced by the peak systolic pressure, which is more readily obtained.

Methods

Eleven patients with coronary heart disease and one patient with congestive cardiomyopathy were investigated during diagnostic cardiac catheterization (table 1). Informed written consent was obtained before the investigation. The patients were studied in the postabsorptive state and 10 mg of diazepam were given orally 1 hour before the catheterization.

A catheter-tip manometer (10 patients) or a pigtail catheter (two patients) was placed in the left ventricle by the femoral or brachial approach. The aortic pressure was measured through fluid-filled catheters. A pacing catheter was advanced into the right atrium. After positioning of the catheters, propranolol, 0.15 mg/kg, and atropine, 1 mg, were given i.v. to minimize changes of myocardial contractility mediated through the autonomous nervous system.

Ten minutes after propranolol and 5 minutes after atroin administration, monoplane left ventriculography was performed in the 30° right anterior oblique projection by injecting 40 ml of Urographin 76 at a flow rate of 10 ml/sec. Ten minutes after the first ventriculogram, 10 mg of isosorbide dinitrate (ISDN) were given sublingually. Arterial pressure was recorded, and when peak systolic pressure had decreased by at least 15 mm Hg, ventriculography was repeated identically. Fifteen minutes later, an i.v. infusion of methoxamine was started at a rate of 2 mg/min. When the peak systolic pressure had reached
a level that exceeded peak systolic pressure during the first ventriculogram by more than 10 mm Hg, ventriculography was repeated again in unchanged projections. In patient 12, the left ventricular peak pressure increased by only 7 mm Hg during methoxamine infusion compared with control. Whenever heart rate decreased by more than 6 beats/min during pressure loading, atrial stimulation was initiated at the rate at which the first angiogram was obtained. Atrial stimulation was instituted according to this criterion in eight patients.

In eight patients, two left ventricular angiograms each showed a single extrasystole induced by manipulation of the injection catheter. The P-V<sub>es</sub> relation was also determined with the postextrasystolic beats in these patients to study the influence of a positive inotropic intervention on a beat-to-beat basis (i.e., postextrasystolic potentiation).

The end-systolic pressure was determined as the pressure of the dicrotic notch in the aortic pressure tracing. In the first three patients, a phonocardiogram was recorded to determine the moment of aortic valve closure by the aortic component of the second heart sound (A<sub>2</sub>). In these three patients the end-systolic pressure was also measured (catheter-tip monometer) as the left ventricular pressure at aortic valve closure. The maximal difference between the results of the two methods was 5 mm Hg.

Left ventricular volumes and ejection fraction (EF) were calculated from end-diastolic and end-systolic silhouettes using the area-length method. The smallest silhouette was selected as the end-systolic silhouette. Calibration of the angiographic magnification factor was obtained by filming a metal sphere with a diameter of 5 cm, which was placed in the position of the left ventricle. Ventriculography showed that one patient had apical dyskinesis and seven patients had local hypokinesis or akinosis.

Calculations

The three points of the P-V<sub>es</sub> relation (with pressure on the ordinate and volume on the abscissa) were subjected to a linear regression analysis, which yielded the slope k. By solving the regression equation for P = 0, the theoretical volume at zero pressure (V<sub>0</sub>) (i.e., the intercept of the regression line with the abscissa) was calculated. The P-V<sub>es</sub> relations were also calculated using end-systolic volume normalized for body surface area. The same calculations were performed with the peak systolic pressure instead of the end-systolic pressure.

The relation between the slope k and the left ventricular EF as a measure of left ventricular performance was calculated as a linear and exponential function. The paired t test was used for the statistical evaluation of the effects of propranolol and atropine. The effects of ISDN and of methoxamine were analyzed using the Friedman test, which gives only the overall probability of a significant difference between the three conditions under investigation.

Results

After the administration of propranolol and atropine, the heart rate increased from 65 ± 9 (± SD) to 80 ± 9 beats/min (p ≤ 0.01). The left ventricular end-diastolic pressure decreased from 13.9 ± 5.7 to 12.3 ± 5.1 mm Hg. The peak systolic pressure declined from 137 ± 22 to 129 ± 21 mm Hg (p ≤ 0.01).

During ISDN and methoxamine, the heart rate remained within a narrow range (table 1). Peak systolic pressure decreased from 129 ± 21 to 100 ± 19 mm Hg after ISDN and increased to 167 ± 33 mm Hg during methoxamine infusion (p ≤ 0.01). End-systolic pressure changed similarly, but to a lesser degree (control 105 ± 13 mm Hg vs 82 ± 13 mm Hg after ISDN and 134 ± 25 mm Hg during methoxamine). End-diastolic pressure decreased from 12.3 ± 5.1 mm Hg to 6.4 ± 3.6 mm Hg after ISDN and increased above control level to 15.5 ± 6.4 mm Hg during methoxamine infusion (p ≤ 0.01).

During ISDN the end-diastolic volume decreased from a control level of 76 ± 52 ml to 57 ± 29 ml and increased to 95 ± 61 ml during methoxamine infusion (p ≤ 0.01). The end-diastolic volume showed similar changes under the three conditions. Both interventions resulted in minor but significant changes in left ventricular EF, from 60 ± 12% to 63 ± 11% during ISDN and to 57 ± 14% during methoxamine (p ≤ 0.05).

The end-systolic P-V<sub>es</sub> relations show linearity (r = 0.96, least-squares fit), and inspection of figure 1 suggests that the three points for each patient form a straight line. The slope k, however, varies con-
Table 1. Hemodynamic Data and End-systolic–Peak Systolic Pressure-Volume Relation

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>BSA (m²)</th>
<th>HR (beats/min)</th>
<th>EDV (ml)</th>
<th>ESV (ml)</th>
<th>ESVI (ml/m²)</th>
<th>ESP (mm Hg)</th>
<th>PSP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>N</td>
<td>M</td>
<td>C</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>1</td>
<td>58</td>
<td>CHD</td>
<td>2.0</td>
<td>79</td>
<td>75</td>
<td>78</td>
<td>109</td>
<td>83</td>
<td>119</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>CHD</td>
<td>1.95</td>
<td>75</td>
<td>76</td>
<td>79</td>
<td>200</td>
<td>175</td>
<td>191</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>CHD</td>
<td>1.85</td>
<td>62</td>
<td>86</td>
<td>62</td>
<td>196</td>
<td>159</td>
<td>227</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>CHD</td>
<td>1.95</td>
<td>71</td>
<td>71</td>
<td>70</td>
<td>325</td>
<td>278</td>
<td>350</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>CHD</td>
<td>1.81</td>
<td>81</td>
<td>82</td>
<td>83</td>
<td>246</td>
<td>203</td>
<td>292</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>CHD</td>
<td>2.08</td>
<td>79</td>
<td>82</td>
<td>81</td>
<td>109</td>
<td>102</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>CHD</td>
<td>2.07</td>
<td>93</td>
<td>98</td>
<td>95</td>
<td>147</td>
<td>136</td>
<td>170</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>CHD</td>
<td>1.95</td>
<td>87</td>
<td>89</td>
<td>83</td>
<td>174</td>
<td>173</td>
<td>228</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
<td>CMP</td>
<td>2.02</td>
<td>75</td>
<td>73</td>
<td>72</td>
<td>307</td>
<td>165</td>
<td>341</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>CHD</td>
<td>1.9</td>
<td>77</td>
<td>82</td>
<td>80</td>
<td>147</td>
<td>81</td>
<td>165</td>
</tr>
<tr>
<td>11</td>
<td>56</td>
<td>CHD</td>
<td>1.8</td>
<td>85</td>
<td>84</td>
<td>84</td>
<td>113</td>
<td>90</td>
<td>132</td>
</tr>
<tr>
<td>12</td>
<td>53</td>
<td>CHD</td>
<td>1.83</td>
<td>90</td>
<td>92</td>
<td>91</td>
<td>128</td>
<td>124</td>
<td>131</td>
</tr>
</tbody>
</table>

Mean 53 ± 10 ± 9 ± 8 ± 9 ± 75 ± 58 ± 83 ± 32 ± 29 ± 61 ± 25 ± 15 ± 31 ± 13 ± 13 ± 21 ± 19 ± 33

Abbreviations: CHD = coronary heart disease; CMP = congestive cardiomyopathy; BSA = body surface area; HR = heart rate; EDV = end-diastolic volume; ESV = end-systolic volume; ESVI = end-systolic volume index; ESP = end-systolic pressure; PSP = peak systolic pressure; EDP = end-diastolic pressure; EF = ejection fraction; r_Es = correlation coefficient of the linear regression analysis applied on the three data points for the end-systolic pressure-volume relation; k_Es = slope of the end-systolic pressure-volume relation; b_Es = intercept on the ordinate of the end-systolic pressure-volume relation; V_E = intercept on the abscissa of the end-systolic pressure-volume relation; k_i = correlation coefficient of the linear regression analysis of the end-systolic pressure-volume relation using the index of the end-systolic volume; k_L = slope of the end-systolic pressure-volume relation using ESVI; b_L = intercept on the ordinate of the linear regression pressure-volume relation using ESVI; V_L = intercept on the abscissa of the end-systolic pressure-volume relation using ESVI; k_p = slope of the peak systolic pressure/end-systolic volume relation; C = control after administration of propranolol and atropine; N = isosorbide-dinitrate; M = methoxamine.

considerably. The slope k derived from the P-V_es relation correlated linearly (r = 0.89) with the control left ventricular EF. The line intercepts the abscissa, however, at an EF of 45% (fig. 2). Therefore, low EFs are not covered by this linear correlation. An exponential function yields a higher correlation coefficient (r = 0.94) and also encompasses the range of low EFs (fig. 3). When the end-systolic volumes are normalized for body surface area, the results are very similar (table 1). The slope k_l is related to EF:

\[
k_{ES} = \frac{mm \, Hg}{mL} = 0.046 \cdot e^{0.072 \cdot EF} (r = 0.94).
\]

In contrast to the slope k of the P-V_es relation, its intercept on the abscissa, which indicates the theoretical volume at V, did not show a consistent correlation with the control EF (fig. 4). Considerable scatter of the data was also evident (fig. 4) when V, was obtained from P-V_es relations using normalized end-systolic volume (V,). Peak systolic pressure is linearly related to end-systolic volume in a given patient (fig. 5) with a correlation coefficient of at least r = 0.93. The correlation of the slope k_{PS}, which is derived from the relation of peak systolic pressure and end-systolic volume with EF (fig. 6), may be described by a linear function (r = 0.88), but yields a higher correlation coefficient (r = 0.95) with an exponential function (fig. 7).

In the eight patients with single extrasystoles during two ventriculograms, the P-V_es relation of the postextrasystolic beats was displaced to the left (smaller end-systolic volumes) and became steeper (fig. 8).

![FIGURE 2. Linear relation between control left ventricular ejection fraction (EF) and the slope k_Es of the end-systolic pressure-volume relation.](http://circ.ahajournals.org/).
TABLE 1. (Continued)

<table>
<thead>
<tr>
<th>EDP (mm Hg)</th>
<th>EF (%)</th>
<th>kES (mm Hg/ml)</th>
<th>bES (mm Hg)</th>
<th>V0 (ml)</th>
<th>r</th>
<th>k1 (mm Hg/ml)</th>
<th>b1 (mm Hg)</th>
<th>VdI (ml/m²)</th>
<th>rPS (mm Hg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>N</td>
<td>M</td>
<td>C</td>
<td>N</td>
<td>M</td>
<td>rES</td>
<td>(mm Hg/ml)</td>
<td>(mm Hg)</td>
<td>(ml)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>11</td>
<td>71</td>
<td>70</td>
<td>66</td>
<td>0.99</td>
<td>5.50</td>
<td>-56.8</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>9</td>
<td>24</td>
<td>47</td>
<td>58</td>
<td>38</td>
<td>0.99</td>
<td>0.65</td>
<td>67.9</td>
<td>-104</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>12</td>
<td>55</td>
<td>57</td>
<td>50</td>
<td>0.99</td>
<td>1.37</td>
<td>-22.3</td>
<td>16</td>
</tr>
<tr>
<td>17</td>
<td>13</td>
<td>17</td>
<td>55</td>
<td>62</td>
<td>49</td>
<td>0.96</td>
<td>0.60</td>
<td>13.1</td>
<td>-22</td>
</tr>
<tr>
<td>19</td>
<td>11</td>
<td>28</td>
<td>55</td>
<td>56</td>
<td>53</td>
<td>0.99</td>
<td>1.25</td>
<td>-29.5</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>13</td>
<td>65</td>
<td>66</td>
<td>62</td>
<td>0.99</td>
<td>2.12</td>
<td>18.7</td>
<td>-9</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>13</td>
<td>51</td>
<td>61</td>
<td>51</td>
<td>0.99</td>
<td>1.20</td>
<td>4.7</td>
<td>-4</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>7</td>
<td>75</td>
<td>78</td>
<td>77</td>
<td>0.99</td>
<td>6.35</td>
<td>-165.2</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>20</td>
<td>37</td>
<td>39</td>
<td>34</td>
<td>0.99</td>
<td>0.50</td>
<td>19.7</td>
<td>-39</td>
</tr>
<tr>
<td>17</td>
<td>5</td>
<td>20</td>
<td>73</td>
<td>74</td>
<td>71</td>
<td>0.99</td>
<td>5.40</td>
<td>-90.4</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>9</td>
<td>57</td>
<td>60</td>
<td>54</td>
<td>0.99</td>
<td>1.13</td>
<td>36.0</td>
<td>-32</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>12</td>
<td>75</td>
<td>76</td>
<td>74</td>
<td>0.99</td>
<td>4.50</td>
<td>-53.3</td>
<td>12</td>
</tr>
</tbody>
</table>

Discussion

The methodologic limitations of this study should be considered. First, monoplane ventriculography is inferior to the biplane technique for the measurement of the end-systolic volume, especially in the presence of local asynergy. We used the monoplane technique because only one patient had a dyskinetic segment in the ventriculogram and because the difference rather than the absolute values of the end-systolic volumes is used to calculate the slope k of the P-Ves line. Therefore, an error of the volume determination, which presumably affects all three measurements in the same patient in a similar manner, would not greatly affect the calculation of the slope k. Second,
the definition of end-systole remains problematic. We derived end-systolic volume from the smallest left ventricular silhouette, which was presumably permissible because no patient had mitral incompetence. The end of ejection was therefore assumed, on the basis of animal experiments, to coincide with end-systole.

Third, the dicrotic aortic notch pressure can be considerably higher than the simultaneous left ventricular pressure in the dog, which is probably due to deceleration of ejected blood. In the three patients in whom left ventricular pressure was measured, a phonocardiogram was recorded simultaneously. The aortic component of the second heart sound \(A_2\) was taken as the moment of aortic valve closure. The maximal difference between the dicrotic notch pressure and left ventricular pressure at \(A_2\) was 5 mm Hg. The dicrotic notch pressure tended to be higher than the left ventricular pressure at \(A_2\). As the slope \(k\) of the P-V\(_{es}\) line is calculated with the difference of the end-systolic pressures and not with the absolute pressure values, the error induced by the use of dicrotic notch pressure is very small. We used aortic dicrotic notch pressure as end-systolic pressure in accordance with Grossman et al. because the technically more difficult measurement of left ventricular pressure using a catheter-tip manometer during angiography is avoided.

The linearity of the P-V\(_{es}\) relation has been shown in experimental studies. The slope of this line increased with positive inotropic interventions. Grossman et al. showed that the slope of the P-V\(_{es}\) relation can be used to separate patients with depressed left ventricular function from those with normal left ventricular performance as judged by EF, although the groups overlapped. Grossman et al. used only two points to calculate the P-V\(_{es}\) relation, assum-
The intercept of the P-V_{es} line on the abscissa represents the theoretical volume at V_{0} and has been proposed as a measure of left ventricular function. We could not confirm these findings. Although the P-V_{es} line is shifted to the right with decreasing left ventricular performance, the slope is often diminished to an even higher degree, so that the intercept on the abscissa may fall into or even below the V_{0} range of left ventricles with normal function (fig. 4). This also applies to P-V_{es} lines calculated with end-systolic volumes normalized for body surface area (fig. 4). One possible explanation for the discrepancy with the study of Grossman et al. could be that in their study, the ventricles were volume-loaded due to mitral regurgitation in 12 of 19 patients. The volume load tends to shift the P-V_{es} relation toward higher volumes than impaired myocardial function due to coronary heart disease without valvular abnormalities. Further, in the study of Grossman et al. the group with the worst left ventricular function consisted mainly of patients with congestive cardiomyopathy, which may explain the high end-systolic volumes and consequently the high V_{0} values in this group.

To study the effects of acute inotropic interventions, we constructed P-V_{es} lines from two postextrasystolic beats, which were steeper and displaced to the left toward smaller volumes as compared with P-V_{es} relations from normal beats (fig. 8). This observation is preliminary, because one cannot assume that the two analyzed postextrasystolic beats, which follow randomly induced extrasystoles, have the same inotropic state. But we felt justified to draw cautious conclusions from this type of analysis, because we found, in accordance with Markis et al., that neither the coupling interval nor the length of the postextrasystolic pause determines the postextrasystolic increase of the EF to a significant degree.

Thus, the P-V_{es} relation has advantages as a measure of left ventricular function: It is independent of afterload because afterload variation is an operational means to establish the P-V_{es} relation. According to the studies of Suga et al. and Mahler et al., the P-V_{es} relation is independent of preload. The relation between the slope k and EF is fairly steep in the range of borderline depression of left ventricular EF (50–60%), so that the P-V_{es} relation may detect slight impairment of left ventricular function more sensitively than EF at rest.

We conclude from this study that the P-V_{es} relation appears to be linear in man. One may estimate the slope k from two P-V_{es} data points if there is a reasonably large difference between the V_{es} values. The slope k of the P-V_{es} relation detects mild left ventricular depression quite sensitively and responds to acute inotropic interventions (e.g., postextrasystolic potentiation). The intercept on the abscissa that represents the theoretical end-systolic volume at zero pressure does not separate normal ventricles from those with impaired performance, at least in this small study group with normal valvular function. The end-systolic pressure can be replaced by the peak systolic pressure, which is technically easier to obtain.
References

The linearity of the end-systolic pressure-volume relationship in man and its sensitivity for assessment of left ventricular function.
H C Mehmel, B Stockins, K Ruffmann, K von Olshausen, G Schuler and W Kübler

Circulation. 1981;63:1216-1222
doi: 10.1161/01.CIR.63.6.1216

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/63/6/1216

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/