Studies of Cardiopulmonary Blood Volume

Measurement of Left Ventricular Volume by Dye Dilution

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SUMMARY

The measurement of ventricular end-diastolic volume from washout of an indicator requiring blood sampling was studied in a heart model and in dogs and applied to the left ventricle in 34 human subjects. The model, under the ideal conditions of constant ejection fraction, uniform cycle length, and complete or nearly complete mixing, demonstrated that dye dilution accurately measures chamber volumes if the distorting effects of catheter sampling are obviated by clearance of the sampling system at least once per two cardiac cycles. The studies in dogs and in human beings demonstrated that the required sampling conditions are achievable.

In 11 normal human subjects, left ventricular end-diastolic volume ranged from 72 to 99 with a mean of $82 \pm 12$ ml/m,$^2$ end-systolic volume, from 22 to 60 with a mean of $37 \pm 11$ ml/m,$^2$ and ejection fraction, from 0.39 to 0.71 with a mean of 0.55 $\pm$ 0.08. These measurements are in substantial agreement with results by radiocardiography and thermal dilution and are systematically, but only slightly, higher than results by quantitative angiocardiography.

In six considerably older patients with chronic pulmonary disease, cardiac output was normal for the age group but ejection from a ventricle of normal size was reduced. In 12 subjects with pure mitral stenosis and in five with atrial septal defect, end-diastolic volume and ejection fraction were significantly reduced.

End-diastolic volume correlated with stroke volume in all groups and in the series as a whole, but a correlation between end-diastolic volume and cardiac output was demonstrated only in the patients with mitral stenosis or atrial septal defect. This suggests that chronic restriction to ventricular filling results in decreased end-diastolic volume. The absence of a significant correlation between end-diastolic volume and end-diastolic pressure indicates that variation in ventricular compliance precludes reliance on end-diastolic pressure as a valid index of end-diastolic fiber length.

Additional Indexing Words:
Chronic pulmonary disease
Mitral stenosis
Atrial septal defect
Ventricular compliance

MEASUREMENT of the volume of blood in individual cardiac chambers is possible by two techniques: angiocardiography and indicator dilution. The latter should be ideal since it requires no geometric assump-

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MEASUREMENT OF LEFT VENTRICULAR VOLUME

one study of left ventricular dimensions.\textsuperscript{5} This paucity of measurements was due, in part, to doubts about ventricular mixing but, of more importance, to a lack of confidence in the fidelity of techniques which require catheter sampling. The latter consideration has led to the use of indicators detectable with intravascular sensors, such as heat\textsuperscript{6,7} and ascorbate.\textsuperscript{8} However, although these indicators have advantages specific to ventricular volume measurement (rapid response time and limited recirculation), neither is an ideal intravascular indicator, since ascorbate is metabolically active and heat may exchange with chamber and vessel walls.\textsuperscript{9} Therefore, in our studies of circulatory volumes, previous aspects of which have been reported elsewhere,\textsuperscript{10,11} we elected to attempt left ventricular volume measurements using a conventional optical indicator which, because it is easily quantified and truly intravascular, is applicable to all flow and volume measurements based on the indicator-dilution principle.

The present study was undertaken to determine whether measurements of left ventricular volume, using such an indicator, were valid, reliable, and feasible in man and, if so, to offer values in normal human subjects for comparison with results by angiocardiography, radiocardiography, and thermal dilution.

**Methods**

Experiments were performed first in a model to determine the sampling conditions which would permit valid measurement of known volumes. The model was identical with that used in previous studies from this laboratory,\textsuperscript{12} except that, to ensure mixing, the ventricle contained an iron bar which was agitated by a rotating magnet. Indocyanine-green dye was introduced into the ventricle during diastole, and dilution curves were sampled through a needle positioned just distal to the aortic valve and connected to the cuvette of a Gilford densitometer. The output of the densitometer was recorded with an oscilloscopic recorder (Electronics for Medicine). The combined volume of needle, an adapter, and the cuvette was 0.22 ml. Sampling was by means of Harvard withdrawal pumps at rates of 1.5 to 75 ml/min. The corresponding 90% response times to a square wave input of dye\textsuperscript{13} ranged from 0.43 to 10.8 seconds. A total of 44 measurements was made at 11 sampling rates.

For each dilution curve, concentration was plotted semilogarithmically as a function of stroke number. Except for the initial 1 or 2 beats on some curves, concentrations uniformly fell on a single slope of exponential decay. From each curve, the ejection fraction, which is the ratio of stroke volume to end-diastolic volume, was calculated as $1 - \frac{C_{N+1}}{C_N}$, where $C_N$ is the concentration on any beat, $C_{N+1}$ the concentration on the succeeding beat, and the concentration ratio $\frac{C_{N+1}}{C_N}$ is obtained as the kth root of 0.1 where k is the number of beats required for a one decade fall in concentration. End-diastolic volume (EDV) was calculated by dividing stroke volume, which was fixed at 5.0 ml/beat, by the measured ejection fraction.

To express the sampling system characteristics, we used the idea, suggested by Sherman and associates,\textsuperscript{14} of a figure of merit representing the number of beats elapsing during the time required to clear the system. This number may be calculated as $(V \times R)/Q$ where V is the volume of the sampling system, R the pulse rate, and Q the sampling rate. It will be evident that response time is a function of V and Q while figure of merit is a function both of response time and of the frequency of the phenomenon to be measured. Figure 1 illustrates the character of the curves obtained in the hydraulic model and demonstrates that, with a figure of merit of 0.09 beats (that is, with a sampling system cleared approximately 10 times per beat) there is only a small error in measurement of EDV. Sherman and his associates, on the basis of theoretic considerations, predicted significant distortion of the dilution curve if the sampling system were not cleared within a time interval corresponding to less than two cardiac cycles. Our data, summarized in figure 2, provide experimental verification of Sherman’s prediction and, moreover, demonstrate that the distortions associated with figures of merit between one and two produce percentage errors of entirely acceptable magnitude. This is of special importance in view of the fact that such figures of merit are readily achievable in man. With a sampling dead space of 2.0 ml, for example, withdrawal at 120 ml/min should suffice for all heart rates up to 120/min and, with a dead space of 1.0 ml, withdrawal at 120 ml/min should suffice for heart rates up to 240/min.

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Dilation curves recorded in the hydraulic model. In this and all other figures, time lines are at 1-sec intervals and paper speed is 5 mm/sec. The curves above were obtained with a sampling rate of 75 ml/min. They illustrate the characteristics of the recordings obtained in the model and also the frequently observed disparity between peak concentrations with virtual identity of later concentrations.

EDV = 7.2 ml.  
FIGURE OF MERIT = 0.09 beats  
CALCULATED EDV = 7.0 ml.

Figure 1

The percentage error in calculation of end-diastolic volume in the hydraulic model as a function of figure of merit.

Studies were then performed in dogs to ascertain whether mixing and the fraction of EDV ejected per beat were sufficiently constant to permit reproducible measurements in the living heart. In mongrel dogs, anesthetized with intravenous pentobarbital (25 mg/kg of body weight) or with intraperitoneal morphine sulfate (3 mg/kg) followed by intravenous chloralose (10 mg/kg), 6F NIH catheters, 50 cm long, were inserted through the brachiocephalic trunks into the left ventricular apex and the aortic root just distal to the valve. Sudden injections of indocyanine-green dye were made into the left ventricle, and blood was sampled from the aorta through the densitometer by means of Harvard pumps at rates up to 150 ml/min. The sampling system volume, including the densitometer cuvette, was 0.9 ml, and the 90% response times of the sampling system ranged from 0.45 to 0.60 second. For some of the measurements, the time constant of the Gilford densitometer was shortened and the corresponding 90% response times diminished to 0.23 to 0.3 second. The use of different anesthetic schedules permitted measurements to be made at heart rates ranging from 30 beats/min, corresponding to the pulse rate of the hydraulic model, to 172 beats/min, representing a significantly higher rate than is seen in exercising human subjects. Figure 3 shows the character of curves recorded in the dog at a sampling rate achievable through the 70-cm length of tubing necessary to reach the aortic root from the brachial artery in man. A step function of change in diastolic concentration per beat is clearly discernible at a heart rate corresponding to that seen in resting man and also in the presence of a tachycardia comparable to that seen in the exercising human subject. Reproducibility (fig. 4) was excellent: the
Ventricular washout curves obtained in dogs. The curve on the left was obtained with a heart rate (84/min) corresponding to that of resting man and that on the right with a heart rate (129/min) comparable to that observed with moderate exercise.

Reproducibility of measurements of left ventricular ejection fraction in the dog. The ejection fraction obtained on a given measurement (on the abscissa) is compared with the fraction obtained on the subsequent measurement (on the ordinate). The coefficient of variation (6%) compares favorably with the value obtained (3%) in the model under nearly ideal conditions of mixing and sampling.

mean coefficient of variation for 82 measurements in 10 dogs was 6% of a measurement, permitting the conclusion that mixing per beat and the fraction ejected per beat are sufficiently constant in vivo to permit highly reproducible measurements of EDV.

The human subjects were 21 males and 13 females, aged 13 to 68 years, with no left ventricular abnormality. Eleven subjects were normal human volunteers and six were patients with pulmonary disease with no demonstrable cardiovascular lesions. The remaining subjects were patients with cardiovascular disease not involving the left ventricle: pure mitral stenosis (12 subjects) and atrial septal defect (five subjects). All except four patients had a regular sinus rhythm. The four exceptions had mitral stenosis and were in atrial fibrillation with a slow and regular ventricular response. Right and left heart catheterization was performed in all subjects. The left ventricular catheter was a Brockenbrough catheter introduced by the transeptal technique in the patients with mitral stenosis, or an NIH catheter (no. 6 or 7F, 80 cm long) passed across the defect in the patients with atrial septal defects or inserted through a right brachial arteriotomy in all others. The aortic catheter was either a polyethylene catheter (I.D., 1.13 mm; length, 70 cm) introduced percutaneously through a brachial artery by the Stille-Seldinger technique or an NIH catheter (no. 6 or 7F, 80 cm long) introduced through an arteriotomy. In all instances, the sampling catheter was passed into the left ventricle and then positioned just distal to the aortic valve by pressure and fluoroscopic monitoring, and the injection catheter was placed near the apex of the left ventricle. Indocyanine green (6.6 mg) was introduced by sudden injection, and blood was sampled at rates of 75 to 120 ml/min. Sampling system dead spaces ranged from 1.0 to 2.1 ml and 90% response times from 0.55 to 0.65 second. A total of 146 curves was obtained in the 34 subjects.

Curves were plotted and ejection fraction calculated as described above. Mean stroke volume, except in patients with atrial septal defect, was obtained from three or more aortic dilution curves following pulmonary arterial injections, which were interspersed among the left ventricle-to-aorta curves. The latter were not used to calculate flow since, for many curves, the initial concentrations were deliberately thrown off scale and, in any event, the vagaries of mixing and infidelity of recording for the first few beats make outputs calculated from such curves suspect. In the patients with atrial septal defect, left ventricular stroke volume was obtained from aortic dilution curves during continuous infusions of dye into the left ventricle, which technique has.
been shown to yield accurate measurements of minute flow,15, 16 EDV for each patient was calculated as the ratio of mean stroke volume to mean ejection fraction.

The results of the study (reproducibility of measurements and differences among various subgroups) were evaluated using conventional statistics for small samples.

Results

The methodological data are illustrated in figure 5, which shows curves from three patients with figures of merit of 1.1 to 1.3. The steps are shallower than in the hydraulic model, reflecting principally the fact that the ratio of systolic to diastolic durations in the model was considerably lower than in man. However, in no instance in the human studies was there difficulty in discerning the exponential fall in diastolic concentration. Reproducibility of measurements of ejection fraction was excellent, the mean coefficient of

\[ \text{Figure 5} \]

*Left ventricular washout curves recorded in human beings.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Body surface area</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac output (L/min/m²)</th>
<th>Stroke volume (ml/beat/m²)</th>
<th>End-diastolic volume (ml/m²)</th>
<th>End-systolic volume (ml/m²)</th>
<th>Ejection fraction</th>
<th>End-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.B.</td>
<td>18</td>
<td>M</td>
<td>1.95</td>
<td>81</td>
<td>3.64</td>
<td>45</td>
<td>94</td>
<td>49</td>
<td>0.480</td>
<td>8</td>
</tr>
<tr>
<td>J.R.</td>
<td>14</td>
<td>M</td>
<td>1.45</td>
<td>114</td>
<td>4.46</td>
<td>39</td>
<td>72</td>
<td>32</td>
<td>0.548</td>
<td>7</td>
</tr>
<tr>
<td>J.W.</td>
<td>19</td>
<td>M</td>
<td>1.70</td>
<td>62</td>
<td>2.92</td>
<td>47</td>
<td>78</td>
<td>31</td>
<td>0.602</td>
<td>11</td>
</tr>
<tr>
<td>M.U.</td>
<td>16</td>
<td>M</td>
<td>1.63</td>
<td>90</td>
<td>4.76</td>
<td>53</td>
<td>75</td>
<td>22</td>
<td>0.707</td>
<td>6</td>
</tr>
<tr>
<td>R.M.</td>
<td>44</td>
<td>M</td>
<td>1.80</td>
<td>80</td>
<td>3.90</td>
<td>49</td>
<td>91</td>
<td>42</td>
<td>0.537</td>
<td>12</td>
</tr>
<tr>
<td>T.W.</td>
<td>22</td>
<td>M</td>
<td>1.56</td>
<td>63</td>
<td>3.22</td>
<td>51</td>
<td>94</td>
<td>42</td>
<td>0.548</td>
<td>11</td>
</tr>
<tr>
<td>G.H.</td>
<td>21</td>
<td>M</td>
<td>2.12</td>
<td>66</td>
<td>2.77</td>
<td>42</td>
<td>77</td>
<td>35</td>
<td>0.548</td>
<td>12</td>
</tr>
<tr>
<td>L.F.</td>
<td>30</td>
<td>F</td>
<td>1.53</td>
<td>96</td>
<td>3.70</td>
<td>39</td>
<td>99</td>
<td>60</td>
<td>0.391</td>
<td>6</td>
</tr>
<tr>
<td>J.C.</td>
<td>14</td>
<td>F</td>
<td>1.40</td>
<td>132</td>
<td>4.11</td>
<td>31</td>
<td>59</td>
<td>28</td>
<td>0.529</td>
<td>10</td>
</tr>
<tr>
<td>M.S.</td>
<td>17</td>
<td>F</td>
<td>1.49</td>
<td>60</td>
<td>2.96</td>
<td>49</td>
<td>81</td>
<td>32</td>
<td>0.605</td>
<td>6</td>
</tr>
<tr>
<td>R.R.</td>
<td>43</td>
<td>F</td>
<td>1.76</td>
<td>69</td>
<td>3.29</td>
<td>48</td>
<td>86</td>
<td>39</td>
<td>0.552</td>
<td>12</td>
</tr>
</tbody>
</table>

Data in the Normal Subjects
### Table 2

**Comparisons among Groups**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mitral stenosis</th>
<th>Atrial septal defect</th>
<th>Chronic pulmonary disease</th>
<th>Normal plus chronic pulmonary disease patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>83 ± 24 (60 – 132)</td>
<td>88 ± 13 (58 – 100)</td>
<td>88 ± 10 (76 – 101)</td>
<td>82 ± 12 (70 – 104)</td>
<td>82 ± 20 (60 – 132)</td>
</tr>
<tr>
<td><strong>Cardiac output (L/min/m²)</strong></td>
<td>3.61 ± 0.65 (2.77 – 4.76)</td>
<td>2.35 ± 0.52 (1.93 – 4.00)</td>
<td>2.46 ± 0.75 (1.80 – 3.74)</td>
<td>2.93 ± 0.45 (2.21 – 3.28)</td>
<td>3.37 ± 0.66 (2.21 – 4.76)</td>
</tr>
<tr>
<td><strong>Stroke volume (ml/beat/m²)</strong></td>
<td>45 ± 6 (31 – 53)</td>
<td>27 ± 6 (21 – 42)</td>
<td>29 ± 12 (19 – 49)</td>
<td>36 ± 6 (29 – 46)</td>
<td>42 ± 7 (29 – 53)</td>
</tr>
<tr>
<td><strong>End-diastolic volume (ml/m²)</strong></td>
<td>82 ± 12 (72 – 99)</td>
<td>71 ± 16 (39 – 91)</td>
<td>67 ± 16 (49 – 91)</td>
<td>85 ± 12 (70 – 102)</td>
<td>83 ± 12 (70 – 102)</td>
</tr>
<tr>
<td><strong>End-systolic volume (ml/m²)</strong></td>
<td>37 ± 11 (22 – 60)</td>
<td>44 ± 14 (18 – 59)</td>
<td>38 ± 5 (30 – 44)</td>
<td>48 ± 9 (38 – 64)</td>
<td>41 ± 11 (22 – 64)</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
<td>0.55 ± 0.08 (0.39 – 0.71)</td>
<td>0.40 ± 0.09 (0.29 – 0.55)</td>
<td>0.42 ± 0.07 (0.39 – 0.54)</td>
<td>0.43 ± 0.05 (0.37 – 0.50)</td>
<td>0.51 ± 0.09 (0.37 – 0.71)</td>
</tr>
<tr>
<td><strong>End-diastolic pressure (mm Hg)</strong></td>
<td>9 ± 3 (5 – 12)</td>
<td>8 ± 4 (3 – 14)</td>
<td>9 ± 3 (6 – 12)</td>
<td>10 ± 3 (6 – 13)</td>
<td>10 ± 2 (5 – 13)</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>23.4 (13 – 44)</td>
<td>41.7 (32 – 59)</td>
<td>33.8 (13 – 45)</td>
<td>53.8 (43 – 68)</td>
<td>34.1 (13 – 68)</td>
</tr>
</tbody>
</table>

All hemodynamic data are presented as mean ± 1 sd and, in parentheses, the range. Mean values which differ significantly from the normal at P < 0.01 are preceded by an asterisk (*) and those which differ at P < 0.05 by a dagger (†).
variation for the 146 measurements in the 34 subjects being 5.1%.

The physiological data are shown in tables 1 and 2 and in figure 6. The data for the normal subjects are listed in table 1, and statistics pertinent to comparisons among groups in table 2. These results may be summarized as follows:

In the normal subjects consisting of seven males and four females with an age range extending from adolescence into middle age, cardiac output, heart rate, and stroke volume corresponded well with values reported in the literature for normal subjects, as summarized by us previously.\(^\text{11}\) Left ventricular EDV ranged from 72 to 99 ml/m\(^2\) with a mean value of 82 ± 12 ml/m\(^2\) and ejection fraction from 0.39 to 0.71 with a mean of 0.55 ± 0.08. There were no significant differences between the male and female members of the group.

The patients with chronic pulmonary disease were characterized by reduced cardiac output, stroke volume, and ejection fraction and by an increase in end-systolic volume and no alteration in heart rate or EDV. It is reasonable to attribute this pattern of reduced ejection from a ventricle of normal size to an age difference since the disparities in mean age and age range are marked. Moreover, the mean cardiac outputs (3.6 L/min/m\(^2\) for the normal group and 2.9 L/min/m\(^2\) for the patients with chronic pulmonary disease) correspond closely to the values reported by Brandonbrener and his co-workers\(^\text{17}\) for groups of normal subjects with mean ages of 22.6 and 54.8 years, respectively. If the changes in the chronic pulmonary disease patients are, in fact, due to a physiological change with aging, rather than to the pulmonary disease, to the effects of the latter on the right ventricle, or to occult left ventricular pathology, then this group may be pooled with the younger normals to yield the values listed in table 2 for a larger group of human subjects with age range extending from 13 to 68 years, with normal left ventricles. This enlarged group differs from the younger normals only in having a slightly lower mean cardiac output, stroke volume, and ejection fraction, none of the differences being statistically significant.

In mitral stenosis and atrial septal defect, end-systolic volume and heart rate did not differ from normal, but output, stroke volume, ejection fraction, and EDV were appreciably and significantly below the values obtained in both the normal volunteers and the expanded normal group (normal volunteers plus chronic pulmonary disease). These hemodynamic differences are not attributable to age differences since the mean age of the mitral and septal defect patients approximates that of the expanded normal group and comparison of subgroups of age-matched patients yielded the same results. Moreover, the mean outputs in both patient groups were significantly below those reported for groups of normal subjects with a comparable mean age.\(^\text{17}\) The differences were not due to abnormal rhythms since the patients with mitral stenosis and atrial fibrillation were not distinguishable from those with sinus rhythm and the septal defect patients all had regular rhythms.

There was no significant correlation, for individual groups or for the entire series, between EDV and end-diastolic pressure (\(r = 0.308, P > 0.05\) for the entire series and \(r < 0.3\) for all individual subgroups).
was also no correlation between EDV and cardiac output for the normal subjects, with or without the inclusion of the older subjects with chronic pulmonary disease (r = 0.198, P > 0.4), but a good correlation between these variables for the patients with mitral stenosis or atrial septal defect (r = 0.752, P < 0.01).

In contrast, all groups exhibited a significant correlation (P < 0.01) between EDV and stroke volume: r = 0.769 for the normal subjects, 0.761 for the patients with mitral stenosis or atrial septal defect, and 0.724 for the entire series (fig. 6). These results demonstrate the intimate relationship between EDV and stroke volume and suggest that chronic impairment in ventricular filling results in diminished ventricular volume.

Discussion

The results of this study permit the following conclusions: (1) Under the ideal conditions of the hydraulic model, in which pulse rate and ejection fraction are fixed, and mixing is complete or nearly so, dye dilution yields accurate measurements of chamber volumes, provided that the distorting effects of catheter sampling are obviated by sufficiently rapid clearance of the sampling system; (2) the sampling conditions required are achievable in man; and (3) mixing (even if incomplete) and the fraction of EDV ejected per beat (even if inconstant) are sufficiently uniform in the living heart to permit reproducible estimates of volume. Thus, a measurement of EDV by dye dilution is valid, in the sense that it is truly a function of stroke volume and of the fraction ejected per beat, and reliable, in the sense that it is highly likely to agree with a prior or subsequent measurement. Whether or not such measurements are accurate is not presently demonstrable, since the demonstration requires simultaneous measurement by an independent technique of proven accuracy. As a result, discussions concerning accuracy, which hinge upon the question of ventricular mixing, invariably become either citations of the evidence that mixing is incomplete,18-20 on the one hand, or arguments based upon the necessary but insufficient criterion of reproducibility, on the other. In the absence of a direct experimental demonstration of accuracy, it is clearly of interest to compare our measurements of EDV with those obtained by other authors and other techniques.

Our measurements are in agreement with those obtained in postmortem hearts and with calculations based on prior in vivo measurements of the cardiopulmonary compartments. In normal adults, Höffelsheim and Robin,21 measuring water displacement of wax casts, found a mean volume of 159 ml or, assuming a mean body surface area of 1.70 m², 94 ml/m² and Hochrein,22 measuring chamber capacity by filling under water pressure, found a mean volume of 130 ml or 76 ml/m². From in vivo studies, if the normal interventricular blood volume11,23 (pulmonary circulation plus left atrium) of 250 ml/m² is subtracted from the total cardiopulmonary blood volume10 (ventricular plus interventricular) of 422 ml/m², one arrives at a combined volume for the two ventricles of approximately 170 ml/m² or 85 ml/m² for each chamber.

Our results are also in agreement with those obtained by radiocardiography and quantitative angiocardiography in normal subjects. Using radiocardiography, Folse and Braunwald5 found a mean EDV of 88 ml/m² in three patients without detectable cardiovascular disease and four with congenital lesions not involving the left ventricle. Using angiocardiography, a value of 88 ml/m² was reported by Miller and Swan24 in nine subjects with normal hearts, aged 9 weeks to 14 years. More recently, Kennedy and his co-workers25 using the method of Dodge in 15 men and seven women without clinical and hemodynamic evidence of heart disease, reported a mean EDV of 70 ± 20 ml/m². The results of Folse and Braunwald and of Miller and Swan differ insignificantly (P > 0.05) from our own, while that of Kennedy and associates is significantly lower (P < 0.05), but by less than 15%, than our value. Large discrepancies previously reported between angiocardiography and indicator dilution have, we believe,
resulted from comparisons which include low angiocardiographic values obtained with general anesthesia, arrested respiration, and positive intrathoracic pressure and high values obtained by indicator (thermal) dilution in subjects who were not truly normal.

Our volumes are lower than those of Wilcken who, using a technique similar to our own, reported the highest value by any method (mean EDV in five subjects without left ventricular disease, 108 ml/m²). However, Wilcken's subjects exhibited a high output state, with a mean cardiac index (4.52 L/min/m²) exceeding all mean values reported for groups of normal subjects by the oxygen Fick method (3.22 to 3.79 L/min/m²), dye dilution (3.20 to 3.76 L/min/m²), and angiocardiography (3.47 to 3.64 L/min/m²).

From this survey we conclude that, in the normal left ventricle, mean EDV measured by dye dilution (present series) or angiocardiography (Folse and Braunwald) lies between 80 and 90 ml/m² higher values having been obtained by thermal dilution in abnormal left ventricles and by dye dilution in unexplained high output states, and that mean EDV measured by angiocardiography lies between 70 and 90 ml/m² (Kennedy and co-workers and Miller and Swan), lower values having been obtained under conditions of positive intrathoracic pressure, arrested respiration, and general anesthesia. Using the means, standard deviations, and numbers of subjects reported in the studies cited, the following statistical conclusion is reached: the probability is greater than 0.95 that mean EDV in a series of normal left ventricles will lie between 74 and 101 ml/m² by indicator dilution and between 61 and 91 ml/m² by angiocardiography. We believe that the difference between these two techniques is real and may be due to the opaque medium which has been shown in our laboratory, using direct myography, to produce a small but systematic and immediate increase in ejection fraction and decrease in end-diastolic and end-systolic fiber lengths. It is probable, therefore, that both techniques measure the prevailing EDV and ejection fraction with creditable accuracy, but that the values are altered by the angiocardiographic technique itself to produce a small but systematic discrepancy.

The finding of a diminished EDV in mitral stenosis is not unexpected. A smaller cavity has been described in standard texts and has been considered to be particularly confined to the inflow portion of the ventricle. Moreover, the characteristic decrease in stroke volume has been attributed to reduced ventricular filling. However, a statistically significant decrease in EDV was not found in prior studies, although the data in several are suggestive. For example, EDV was 8% larger in subjects with no demonstrated heart disease than in patients with mitral stenosis in Wilcken's study and in that of Gorlin and associates. Quite possibly the suggestive difference escaped statistical significance in Wilcken's study because of the small number of subjects and in Gorlin's study because of the large variance in the mitral stenosis group which included patients with widely disparate degrees of severity. Certainly, of the possible interpretations for the correlation between systemic flow and EDV, the most conservative interpretation, since no such correlation was found in normal subjects, would seem to be that chronic restriction to venous return imposes a restriction on diastolic volume. An alteration in ventricular filling probably also underlies the diminished volume found in atrial septal defect. The number of patients with this lesion in prior studies is too small to provide either confirmation or dispute.

In previous studies, stroke volume has been shown by Milnor and his associates to be related to pulmonary (or interventricular) volume and by ourselves to both the total cardiopulmonary blood volume and its interventricular compartment. A weaker relationship also existed between volume and cardiac output in Milnor's report, but this relationship was equivocal in our study of interventricular volume and absent in our study of total cardiopulmonary volume. The present study confirms the previous conclusion.
that it is to the stroke volume in particular that the cardiopulmonary volume and its components are related. It is reasonable to infer that the primary relationship is between stroke volume and EDV, the relationship between interventricular and stroke volumes resulting from the fact that, with most physiological adjustments, the interventricular and ventricular volumes vary together, as we have shown to be the case for hemorrhage.40

The absence of a correlation between EDV and end-diastolic pressure has been noted by previous workers whose material consisted chiefly or exclusively of patients with heart disease.6,7,41 It is evident that considerable subject-to-subject variation in ventricular compliance exists in both the normal and diseased left ventricle. For the diseased ventricle, this conclusion necessitates a reappraisal of the interpretation of end-diastolic pressure in the diagnosis of ventricular failure.42 For all ventricles this conclusion indicates that end-diastolic pressure is not a valid index of end-diastolic fiber length and is of limited value as an index of end-diastolic tension, the preload to ventricular contraction.

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