Overestimation of Left Ventricular Volume by the Indicator Dilution Technique

By Richard A. Carleton, M.D., Allen F. Bowyer, M.A., M.D., and John S. Graettinger, M.D.

Since the work of Bing and co-workers and the subsequent observations of Holt, the indicator dilution technique has been used to measure ventricular volume. The validity of the technique depends upon thorough mixing of indicator with ventricular blood. However, experimental data have been presented by Irisawa et al. and subsequently by Swan and Beck suggesting that requisite mixing does not occur promptly or reliably in the left ventricle. Moreover, Hallermann et al., comparing volume estimates made sequentially by angiography and by indicator dilution, have shown a systematic overestimation of volume by the indicator dilution technique, and have suggested that the cause was incomplete mixing of indicator with ventricular blood. Despite these reports of incomplete mixing, several experimental studies have been reported which rely upon left ventricular volume measurements performed by indicator dilution.

The present study was undertaken to clarify the applicability of the indicator dilution technique to the estimation of left ventricular volume.

Methods

The indicator dilution curves used in this study were obtained by measuring injected sodium ascorbate concentration at a platinum electrode 1 mm from the tip of a second cardiac catheter.

The polarographic circuit used for these measurements is similar to that described by Frommer et al., modified to provide a signal to a low impedance optical galvanometer. This system provides a linear response to known ascorbate concentrations in vitro and in vivo as tested by constant vena caval infusion and pulmonary arterial sampling. The response characteristics have been tested in vitro by near square increments or decrements in concentration and in vivo by bolus injections of ascorbate into the aorta 1 cm proximal to the platinum electrode on a separate catheter. In each test situation, the system reached 67% of maximum deflection in 0.3 seconds, and 95% in 0.6 seconds. The polarographic circuit is not calibrated because the sensitivity varies slightly from patient to patient and because only changes in concentration are used.

The indicator dilution curves provided the dimensionless ratio of concentrations (C) for any two successive beats, n and n + 1, after injection of indicator into the left ventricle. An average value for the ratio $C_{n+1}/C_n$ was obtained from the successive steps of end diastolic concentration on the exponential decay limb of each dilution curve, starting with the third cycle after injection. We have termed the complement of this average ratio $1 - (C_{n+1}/C_n)$ the washout slope.

As described by Holt, if indicator is thoroughly mixed in the left ventricle, this ratio can be used to calculate end diastolic volume by the equation

$$EDV = \frac{SV}{1 - \frac{C_{n+1}}{C_n}}$$

For this study, stroke volume (SV) was obtained from the heart rate and cardiac output. The latter was measured by the classical Fick principle, as previously described. End systolic volume was obtained by subtraction of stroke volume from end diastolic volume. Because the accuracy of end diastolic volumes obtained by indicator dilution was the subject of this study, we have chosen the term washout volume in place of indicator dilution end diastolic volume.

In the first phase of this study, volume estimates by indicator dilution were compared with
those obtained by angiocardiography in two to five studies in each of six dogs. Dogs weighing between 11 and 17 kg, were anesthetized with 25 mg/kg of sodium pentobarbital administered intravenously and were studied in the left lateral decubitus position. One catheter was passed into the pulmonary artery, a platinum electrode catheter was positioned approximately 1 cm above the aortic valve and a third no. 7 French catheter with six radial holes and a sealed tip was passed retrograde into the left ventricle.

Fick outputs were obtained with a two-minute expired air collection, during which blood samples were obtained for oxygen analysis. Immediately at the end of each air collection, 2.0 ml of sodium ascorbate were injected in less than 0.7 sec into the mid-portion of the left ventricle for each of two dilution curves recorded from the aorta. The first curve was recorded just prior to, and the second during, the injection of 1.5 ml/kg of sodium diatrizoate (Hypaque), 50%, into the pulmonary artery. The washout slopes of these two curves were averaged. Correction factors for radiographic geometric distortion were determined by means of a modification of the technique of Dodge et al. Radiopaque rulers perforated precisely at 1 cm intervals were fixed to the anterior, posterior, right and left surfaces of the thorax. From the radiographic images of these rulers on both frontal and lateral films, correction factors could be computed without measurements external to the emulsion surface itself.

Measurements of end diastolic and end systolic volume were performed by either of two techniques. The first utilized an Elema-Schonander biplane X-ray film changer exposing six frames per second. Computation of the left ventricular volume from the biplane X-ray exposures was done by a modification of the method of Arvidsson, assuming that ventricular shape can be approximated by a three-dimensional ellipsoid. The spatial length of the major semi-axis (a) was calculated from distortion-corrected measurements of the opacified left ventricle and was used with corrected measurements of the minor semi-axes (b, c) in the equation:

\[ V = \frac{4}{3} \pi abc \]

Pairs of X-ray films were selected, by comparison with simultaneously recorded left ventricular pressure, to represent end diastolic and end systolic volumes. The second technique utilized single plane cineangiographic exposures made with the dog rotated into a slightly right anterior oblique position. Computations for single plane angiocardiograms were done by a modification of the method of Gribbe et al, assuming equality of the two minor semi-axes, and without subtraction of papillary muscle volume. From biplane angiocardiography of the dogs used in this study, the ventricular major axis was found to be approximately parallel to the central sagittal plane and approximately perpendicular to the coronal plane. The plane parallel to the lateral film surface, passing through the center of volume of the left ventricular ellipsoid, closely approximated this central sagittal plane. This simplified greatly the calculations performed with single plane cineangiography. With each technique several (three to six) cycles were analyzed and the average value was taken for end diastolic and end systolic volume. Measurements were not made after the onset of bradycardia which occurs commonly six to eight seconds following left ventricular opacification. Calculations were not performed on any cardiac cycles resulting from premature ventricular contractions.

The second phase of the study was designed to test the uniformity of indicator dispersion in the left ventricle. Sodium ascorbate was injected into the left ventricle as described previously and the rate of concentration decay, expressed as washout slope, was analyzed for two anatomic portions of the ventricle. In a series of five dogs, the sampling electrode was positioned sequentially in three positions; (a) in the outflow tract approximately 1.5 cm below the aortic valve plane, (b) within 1 cm of the apical portion of the left ventricular wall and, (c) in the aorta 1 cm above the aortic valve. Eight to twelve groups of curves were recorded from each site with sets of four curves obtained in rotation in each site to minimize the effect of passing time.

Patients with three kinds of cardiac abnormality were tested in similar fashion. Seven patients had either mitral or valvular aortic stenosis; two patients had partial division of their left ventricular cavity by muscular subaortic stenosis; and two patients had severe aortic regurgitation. Patients were sedated with 50 to 100 mg of pentobarbital given orally and 25 to 75 mg meperidine intramuscularly and were studied in the supine position. Injections were made into the left ventricle; sampling was done with an electrode catheter either in the outflow tract or near the ventricular apex. Six to twelve curves were obtained from each site in alternating groups of three. The average of the washout slopes obtained in each subject at the outflow tract was compared with that obtained at the apex, and the differences were tested by t test.

The directional changes of washout volume following various interventions were tested in the third portion of the study. Two dogs weighing 18 kg (dog A) and 13 kg (dog B) were anesthetized and subjected to thoracotomy. A 16 mm
The data obtained during the eighteen comparative studies of volume are given in table 1. Mean stroke volume calculated by the Fick principle was $13.4 \pm 0.9$ ml and was not significantly different from that calculated by the angiocardiographic technique ($13.0 \pm 0.9$ ml). The primary datum from each pair of dilution curves, the average washout slope, was then compared with the ratio of stroke volume to end diastolic volume of each dog was expanded with 200 ml increments of 5% dextran. The information recorded is shown in figure 1. Three to six dilution curves were recorded from the ascending aorta after injection into the mid-left ventricle in each condition of the animal. Simultaneous measurements were made of washout slope, stroke volume, to permit calculations of washout volume, and of ventricular circumference.

**Results**

I. The data obtained during the eighteen comparative studies of volume are given in table 1. Mean stroke volume calculated by the Fick principle was $13.4 \pm 0.9$ ml and was not significantly different from that calculated by the angiocardiographic technique ($13.0 \pm 0.9$ ml). The primary datum from each pair of dilution curves, the average washout slope, was then compared with the ratio of stroke volume to end diastolic volum

*Medicon model K-2000, Medicon Corporation, Los Angeles, California.*
### Table 1

**Comparison of Washout Volumes and Angiocardiographic Volumes**

<table>
<thead>
<tr>
<th>Dog no. and weight</th>
<th>Washout slope</th>
<th>Stroke volume (Fick)</th>
<th>End diastolic washout volume</th>
<th>End systolic washout volume</th>
<th>Stroke volume (Angiocardiographic method)</th>
<th>End diastolic volume</th>
<th>Stroke volume</th>
<th>End diastolic volume</th>
<th>End systolic volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 18</td>
<td>0.21</td>
<td>10</td>
<td>49</td>
<td>33</td>
<td>0.38</td>
<td>13</td>
<td>36</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>2 15</td>
<td>0.27</td>
<td>15</td>
<td>60</td>
<td>50</td>
<td>0.43</td>
<td>16</td>
<td>38</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>3 15</td>
<td>0.31</td>
<td>14</td>
<td>52</td>
<td>47</td>
<td>0.50</td>
<td>18</td>
<td>36</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>4 14</td>
<td>0.34</td>
<td>17</td>
<td>52</td>
<td>35</td>
<td>0.56</td>
<td>18</td>
<td>32</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>5 16</td>
<td>0.26</td>
<td>12</td>
<td>41</td>
<td>36</td>
<td>0.39</td>
<td>17</td>
<td>43</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>6 11</td>
<td>0.27</td>
<td>13</td>
<td>40</td>
<td>36</td>
<td>0.27</td>
<td>10</td>
<td>38</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>Mean</td>
<td>0.39</td>
<td>13.4</td>
<td>48.3</td>
<td>34.9</td>
<td>0.44</td>
<td>13.0</td>
<td>31.8</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>0.01</td>
<td>0.9</td>
<td>4.3</td>
<td>3.6</td>
<td>0.03</td>
<td>0.9</td>
<td>2.2</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 2
End diastolic (filled circles) and end systolic volumes (crosses) obtained by indicator dilution were significantly greater than those measured by angiocardiography. The line of unity is shown.

End diastolic and end systolic volumes obtained from the angiocardiograms. The mean values of 0.29 ± 0.01 by indicator dilution and 0.44 ± 0.03 by angiocardiography were significantly different. Direct comparison of end diastolic and end systolic washout volumes with the corresponding angiocardiographic measurement is illustrated in figure 2. The average difference between end diastolic volume estimates obtained by the two techniques was 16.5 ± 4.0 ml (52%), and that between paired estimates of end systolic volume was 16.5 ± 3.8 ml (91%), indicating a major systematic overestimation of volume by the indicator dilution technique.

II. Washout slopes obtained after injection and sampling in the outflow tract of the left ventricle were significantly different from those obtained at the apical portion in each of five dogs, as indicated in table 2. The mean difference between washout slopes at the two sites of sampling was 0.10 ± 0.04. Indicator is washed from the outflow portion significantly more rapidly than from the apical portion of canine left ventricles. When sampling was done from the aorta, the washout slopes were not different following injection either at the apex or in the outflow portion. However, in three of the four dogs in which comparisons were made, the washout slopes were smaller with aortic sampling than with sampling in the outflow tract, suggesting the occurrence of change of indicator concentration above the aortic valve beyond that occurring below the valve.

The results of similar studies in three groups of patients are illustrated in figure 3. The washout slopes were significantly (P < 0.05) more rapid when injection and sampling were performed in the outflow tract than in the apical portion of the left ventricle in each of the seven patients in the first group. Injection and sampling in the mid-portion of the left ventricle in one patient (B. C.) gave an average washout slope which was intermediate (0.57 ± 0.05) between those obtained at the apex or in the outflow tract. The two patients with muscular subaortic stenosis had large discrepancies in washout slopes obtained above and below the stenotic area. Conversely, two patients with the enhanced intraventricular mixing of severe aortic regurgitation did not have significantly different washout slopes at the two poles of their left ventricles.

III. The comparison of changes in washout volume with changes in an independent measure of left ventricular size is shown in

<table>
<thead>
<tr>
<th>Injection sites→</th>
<th>Apex</th>
<th>Apex</th>
<th>Outflow</th>
<th>Outflow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling sites→</td>
<td>Apex</td>
<td>Outflow</td>
<td>Apex</td>
<td>Aorta</td>
</tr>
<tr>
<td>Dog 7</td>
<td>0.109 ± 0.007*</td>
<td>0.154 ± 0.009</td>
<td>0.143 ± 0.010</td>
<td>0.141 ± 0.008</td>
</tr>
<tr>
<td>Dog 8</td>
<td>0.203 ± 0.015</td>
<td>0.260 ± 0.009</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dog 9</td>
<td>0.328 ± 0.010</td>
<td>0.483 ± 0.027</td>
<td>0.390 ± 0.018</td>
<td>0.375 ± 0.005</td>
</tr>
<tr>
<td>Dog 10</td>
<td>0.456 ± 0.012</td>
<td>0.499 ± 0.008</td>
<td>0.435 ± 0.006</td>
<td>0.437 ± 0.007</td>
</tr>
<tr>
<td>Dog 11</td>
<td>0.149 ± 0.006</td>
<td>0.384 ± 0.005</td>
<td>0.449 ± 0.010</td>
<td>0.468 ± 0.008</td>
</tr>
</tbody>
</table>

*Mean ± SE.

Circulation Research, Vol. XVIII, March 1966
figure 4. Each expansion in blood volume produced an increase of left ventricular circumference and a corresponding increase of left ventricular washout volume. In dog A the washout volume changed from an average of 38 ml to 74 ml. Vena caval constriction produced approximately similar decreases in washout volume and in circumference at each level of blood volume. The graduated increase in blood volume by 600 ml of dextran in dog B was associated with an increase of washout volume from 28 ml to 43 ml.

Discussion

The precision of the angiocardiographic method for measuring left ventricular volume has been analyzed in several studies, in none of these did radiographically calculated volumes differ by more than 13% from the known volume of a model regardless of the projection used. Spherical and ellipsoidal radiopaque containers have been measured directly and radiologically in our laboratory with comparable results. The average discrepancies between angiocardiographic and in-

![Graph of Washout Slopes](image1)

**FIGURE 3**

Washout slopes obtained following injection and sampling in the outflow tract (open circles) are contrasted with those obtained at the left ventricular apex (A) in the three groups of patients.

![Graph of Comparison of Washout Volume and Circumference](image2)

**FIGURE 4**

Comparison of washout volume (circles) with ventricular circumference (triangles) in dogs A and B. Circumference is shown in arbitrary units on the right ordinate of each panel.

_Circulation Research, Vol. XVIII, March 1966_
Indicator dilution volumes in this study were 52% and 91% for end diastolic and end systolic volumes respectively. Discrepancies of similar magnitude have been reported in a study, also conducted in dogs, by Hallermann, Rastelli and Swan. The possibility that the angiocardiographic technique underestimates true ventricular volume seems remote. Our angiographic technique may indeed overestimate ventricular volume since the intracavitary extension of papillary muscles and of trabeculations, which may represent as much as 33% of the calculated volume according to Gribbe et al., were not subtracted. Moreover, complete analysis of the sequence of volume changes did not reveal an initial decrease in ventricular size prior to the increase associated with bradycardia.

Direct comparisons of ventricular volumes determined by angiography and indicator dilution have not been made in man, but reports of separate series of studies are available. Among individuals considered to have normal left ventricles by the original authors, left ventricular end diastolic volume estimated by indicator dilution averaged 191 ± 13 ml in twelve subjects studied in two series. Data taken from two other reports, in which end diastolic volume was measured by angiocardiography, reveal an average volume of 94 ± 8 ml in fourteen subjects.

In these studies of nearly simultaneous or of separate comparisons, the dilution technique yielded estimates of left ventricular volume in man and dogs which were nearly double the true volume.

Thorough diastolic dispersion of indicator within the left ventricle is necessary if ventricular volume is to be measured precisely by the indicator dilution technique. Two groups of investigators have suggested that the requisite completeness of indicator dispersion does not occur, at least in the first three cycles after injection. The present studies, by demonstrating widely and significantly different rates of indicator washout at the poles of the left ventricle, suggest an hypothesis for intraventricular blood flow. In the left ventricle, flow preferentially occurs along a nearly direct pathway between the mitral valve and the outflow tract. Distal to this favored route, a spectrum of slower routes exists. A markedly slower exchange of blood occurs in the apical cul-de-sac of the ventricle; the slowest extreme of the spectrum of intraventricular flow probably exists in the crevices between trabeculations near the apical portion. The time-concentration curve sampled in the aorta must be a resultant of the indicator originating in the rapidly and slowly washed spaces within the ventricle. The contribution of the areas with relatively slow rates of flow can only prolong the time of concentration decline in the aorta. Thus the inequality of indicator dispersion observed in this study is probably the major cause of volume overestimates obtained by the indicator dilution method.

The observation that washout slopes sampled in the aorta were smaller than those obtained in the outflow tract in three of four dogs suggests that additional indicator dispersion occurred in the proximal ascending aorta. If this mixing occurred with aortic blood containing the higher concentration of indicator which existed during the previous cardiac cycle, the net washout slope would also be slowed. The quantitative role played by aortic mixing in the overestimation of volume has not been defined.

The time available for mixing is of importance in any problem of indicator dispersion. Therefore, on a priori grounds, long ventricular diastolic periods should favor more complete mixing. However, merely to consider the duration of diastole may be misleading because the time available for mixing is not the duration of diastole, but is the time remaining prior to systole after the last volume of blood, including that contributed by atrial systole, has entered the ventricle. In other studies it was found that only a small ventricular volume augmentation was produced by atrial systole at slow heart rates. At more rapid rates, however, the volume contributed by atrial systole was more than 20% of the total. Thus, washout slopes measured at very slow heart rates may more nearly estimate ventricular volume both be-
cause diastolic periods are long and because
the atrial contribution is small. Conversely,
more rapid heart rates, with shorter times for
indicator dispersion and with larger atrial con-
tributions, should be associated with the greatest
overestimates of ventricular volume.

The role of atrial systole is also pertinent
in another approach which has been used to
measure ventricular volume by indicator dilu-
tion. If indicator is injected with sufficient
force to ensure complete mixing during a
single diastole, the concentration attained in
the aorta during the first succeeding systole,
divided into the amount injected, would yield
ventricular volume. Such an injection would
have to be accomplished between atrial and
ventricular systole, however, and satisfaction
of these requirements seems unlikely.

The overall result of these considerations
is that the indicator dilution technique cannot
be used to quantify left ventricular volume;
the term end diastolic volume should not be
applied to the anatomically vague "space"
from which indicator is being washed.

The question whether the washout volume
bears a meaningful relationship to end dias-
tolic volume cannot be answered in broad
terms. In the present study, however, when interventions modified the size of a given
ventricle at a paced heart rate, the washout
volume changed concordantly with actual
changes in ventricular size. An extrapolation
from these studies to other types of changes
in ventricular function in dogs, or to man, is
not warranted. Comparable repetitive studies
utilizing angiocardiography as the standard
of left ventricular volume in man are not
possible both because the technique is un-
pleasant to the subject, and because radio-
paque media themselves modify ventricular
function shortly after their administration.

At best, the indicator dilution method pro-
vides a crude index of ventricular size. The
search must be continued for a method of
measuring ventricular volume repetitively in
man.

Summary
The applicability of the indicator dilution

method to the measurement of left ventricu-
lar volume has been studied. When compared
with angiocardiographic measurements, the
dilution technique overestimates volume by
an average of 52 and 91% in end diastole and
end systole respectively. Studies which dem-
ONstrated more rapid indicator washout from
the outflow than from the apical portion of
human and canine left ventricles suggest
that faulty intraventricular indicator disper-
sion is the major cause of the volume over-
estimates yielded by the dilution method.

The indicator dilution method does not
provide a measure of left ventricular volume,
but may, in carefully designed studies, yield
an index of changes in ventricular size.

Acknowledgment
We are indebted to Mrs. Maxine Yokley for surgical
aid and to Miss Joanne Ford and Mrs. Ethel Burns
for technical assistance.

References
1. Bing, R. J., Heimbecker, R., and Falholt,
W.: An estimation of the residual volume of
blood in the right ventricle of normal and
diseased human hearts in vivo. Am. Heart J.
42: 483, 1951.
of the ventricle of the dog's heart by two indica-
tor dilution technics. Circulation Res. 4: 187,
1956.
3. Ihisawa, H., Wilson, M. F., and Rushmer,
R. F.: Left ventricle as a mixing chamber.
Circulation Res. 8: 183, 1960.
4. Swan, H. J. C., and Beck, W.: Ventricular non-
mixing as a source of error in the estimation
of ventricular volume by the indicator dilution
5. Hallermann, F. J., Rastelli, G. C., and Swan,
H. J. C.: Comparison of left ventricular vol-
umes by dye dilution and angiographic meth-
ods in the dog. Am. J. Physiol. 204: 446,
1963.
6. Bristol, J. D., Crispin, R. L., Farrow, C.,
Harris, W. E., Lewis, R. F., Sutherland,
D. W., and Crishold, H. E.: Left ventricular
volume measurements in man by thermodilu-
7. Gorlin, R., Rollett, E. L., Yurchak, P. M.,
and Elliott, W. C.: Left ventricular volume

Circulation Research, Vol. XVIII, March 1966
Overestimation of Left Ventricular Volume by the Indicator Dilution Technique
Richard A. Carleton, Allen F. Bowyer and John S. Graettinger

Circ Res. 1966;18:248-256
doi: 10.1161/01.RES.18.3.248

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/18/3/248

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
Circulation Research 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 Research is online at:
http://circres.ahajournals.org/subscriptions/